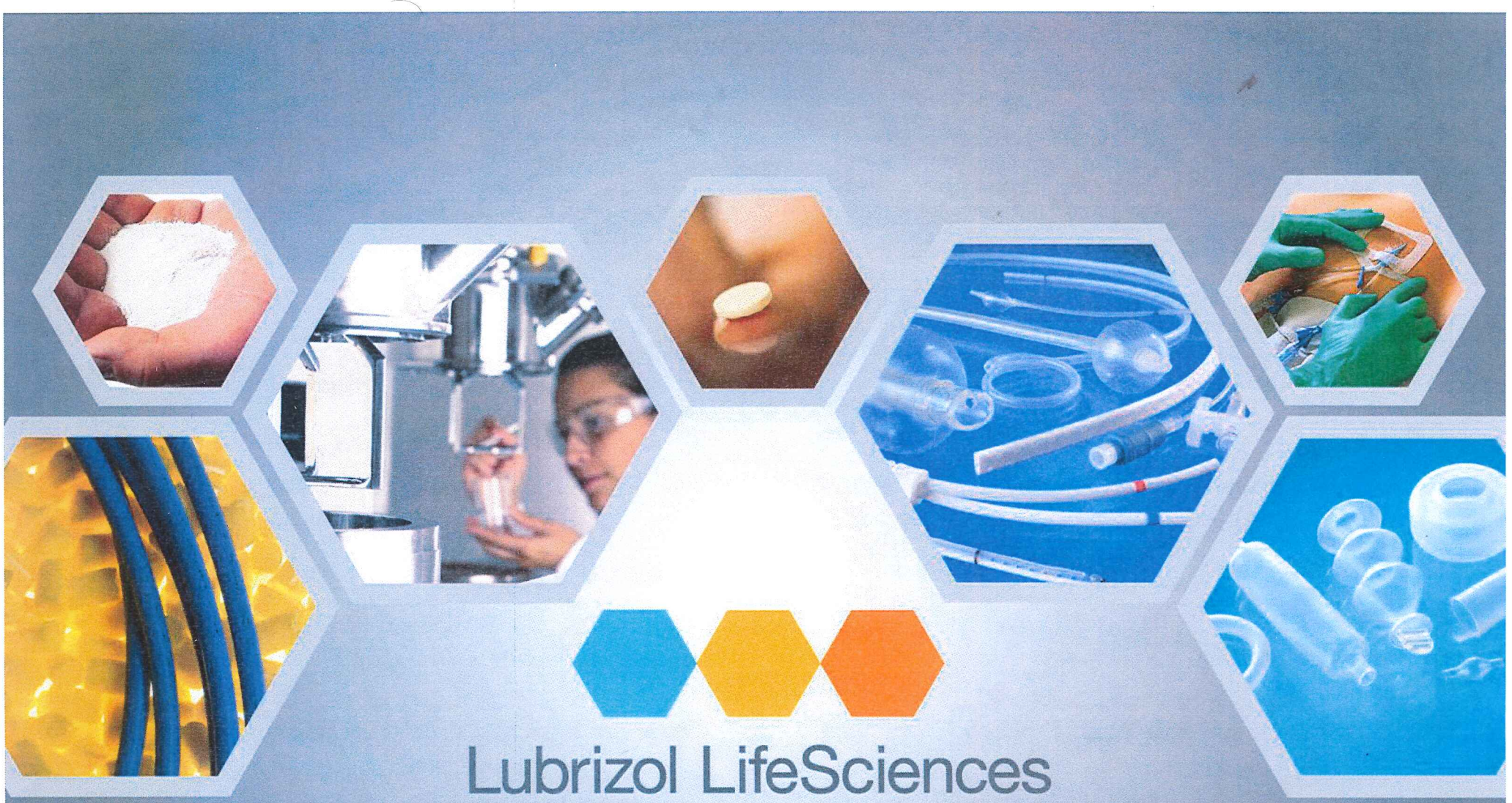
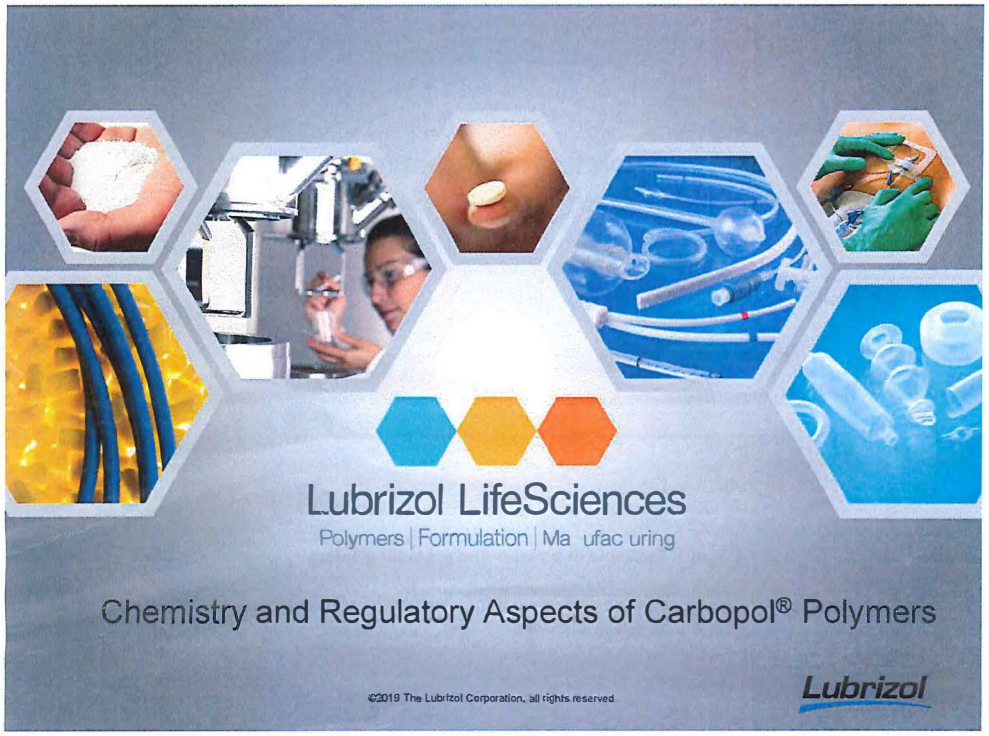


Lubrizol LifeSciences

Polymers | Formulation | Manufacturing

Chemistry and Regulatory Aspects of Carbopol® Polymers

Lubrizol



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Polymers | Formulation | Manufacturing

Outline

- Introduction to pharmaceutical excipients
- Chemistry & structure
- Classification based on chemistry
- Complete list of pharmaceutical range of Carbopol® Polymers
- Classification based on markets, polymerization solvent and site of administration
- Global regulatory status of Lubrizol polymers
- Inactive Ingredient Database of US FDA entries for Carbomers, Polycarbophil and Carboxypolymethylene
- Regulatory support by Lubrizol Lifesciences
- LifeScience Polymers website documents
- Global Excipient Information Package (EIP) documents
- All carbomers are not equal

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Excipients as critical formulation components

- The word *excipient* is derived from the Latin *excipere*, meaning 'to except', which is simply explained as 'other than'. Pharmaceutical excipients are basically everything other than the active pharmaceutical ingredient in a dosage form
- Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system
- Directive 2011/62/EU (Falsified Medicines Directive) gives the first 'legal' definition of 'excipient': Any constituent of a medicinal product other than the active substance and the packaging material
- Pharmaceutical formulations are used for curing ailments and therefore need higher quality standards compared to cosmetic formulations that do not have therapeutic role
- Total number of cosmetic ingredients is about 20,000 versus there are 446 monographs of excipients in the USP NF

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Regulations for Pharmaceutical Excipients

- The manufacturing of Pharmaceutical excipients is regulated by several 'guidance and compliance' documents such as
  - European Pharmacopoeia General Monograph 2034
  - The MHRA orange guide 2017
  - The USP NF General Chapter <1078>
  - The IPEC- PQG Pharmaceutical Excipient GMP
- As against this the manufacturing of API and the Formulations is very well regulated
  - ISO 9001:2008
  - EU GMP for APIs (Eudralex vol IV part 2)
  - 21 CFR parts 210 and 211
  - GMP for finished pharmaceuticals
- Based on the stringent regulations for API and formulations, excipients are also regulated.

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Standards Organizations

Standards Organization	Founded	HQ
ANSI: American National Standards Institute	1918	Washington D.C. USA
NSF: Formerly National Sanitation Foundation, name changed to NSF international in 1990	1944	Michigan USA
ISO: International Organization of Standardization	1947	Geneva, Switzerland
ICH: International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	1990	Geneva, Switzerland
IPEC : International Pharmaceutical Excipient council	1991	Brussels Belgium
IPEC Americas	1991	Virginia, USA
IPEC Europe	1991	Brussels Belgium
IPEC Japan	1992	Tokyo, Japan
IPEC China	2008	Beijing China
IPEC India	2015	Mumbai, India

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Polymers | Formulation | Manufacturing

Application Areas For Lubrizol Products

Tablets and Capsules

- Covalently Crosslinked Polymers
- High Efficiency
- Available in powder and granular grades
- Global regulatory compliances
- Safe and effective

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Polymers | Formulation | Manufacturing

Application Areas For Lubrizol Products

Topical

- Proven rheology modification for Gels, Creams and Lotions
- Versatile and efficient in aqueous, anhydrous and hydroalcoholic systems
- Effective primary emulsifiers and Emulsion stabilizers

Oral Suspensions/Solutions

- Long term stability of Suspensions for a wide pH range
- Highly efficient at low use levels
- Build viscosity and yield value for "non-spill" pediatric formulations
- Taste masking of some bitter tasting drugs

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Polymers | Formulation | Manufacturing

Application Areas For Lubrizol Products

Bioadhesives (Vaginal, Nasal, Oral, Rectal & Ophthalmic)

- Improve bioavailability of active ingredients
- Enhance patient compliance (fewer doses are needed per day)
- Provide excellent adhesive forces
- Lower concentrations of the active ingredient can be used, thereby minimizing potential side effects of the drug

Oral Care

- Efficient co-binders and thickeners at low usage levels
- Suspending agents for non Soluble actives or excipients
- Thicken anhydrous and peroxide Gel systems while maintaining product stability
- Compatible with commonly used formulation ingredients
- Interact with both soft tissue (gum) and hard tissue (enamel)

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Carbopol Polymers

Oral Treatment

- **Tablets and Capsules**
  - IR, ER , Lozenges, Chewable, Buccal
  - Monolithic, Multiparticulate
  - Gastric, Enteric, Colon
  - All four BCS class of drugs
- **Oral Suspensions and solutions**
  - Permanent suspensions
  - Taste masking
  - Bioadhesion
- **Dental /Orthodontic Oral Care**
  - Toothpaste
  - Mouthwash
  - Denture Fixatives
  - Orthodontics

Topical

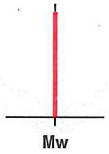
- **Emulgel, Creams, Lotions**
  - Aqueous, anhydrous, hydro alcoholic
  - Broad pH range
  - Rheology and Stability
  - High efficiency, ease of manufacturing
- **Ophthalmic**
  - Suspension
  - Bioadhesion
  - Low preservation
- **Rectal, Vaginal**
  - Rheology, Lubrication
  - Bioadhesion
  - Low preservation

Very Versatile range of polymers for all dosage forms and routes of administration except injectables

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

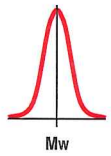
Chemistry and Structure
Acrylic Acid & Polyacrylic Acid

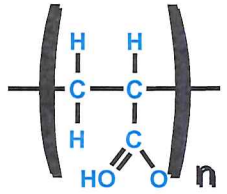
- **Acrylic acid monomer**
  Mw = 72



- $CH_2CH(COOH)$

- **Polyacrylic Acid**
  Mw ~ 603,000

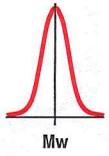




Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

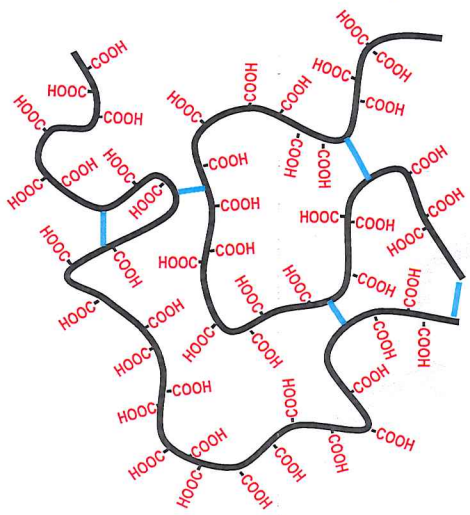
Chemistry And Structure
Carbopol® Homopolymers

- Mw ~ 3.5 billion Daltons



- Crosslinked polyacrylic acid

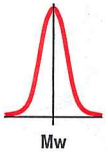
- **Crosslinking agent**
- Polyalkenyl polyether



Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

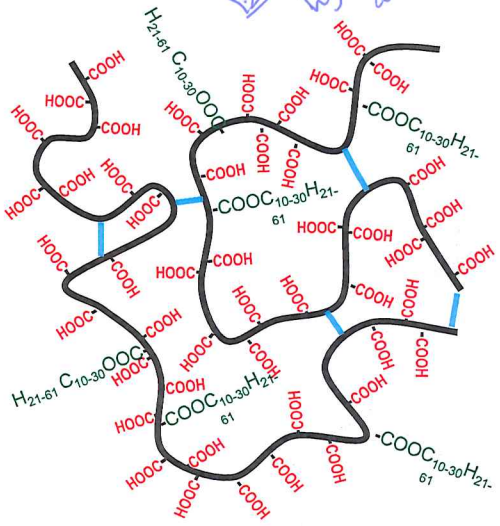
Chemistry and Structure
Carbopol® Copolymers

- Mw ~ 3.5 billion Daltons



- Crosslinked polyacrylic acid

- **Comonomer**
- C_{10} - C_{30} alkyl acrylates



Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Product Type and Regulatory Status

Polymer Chemistry				Pharmacopoeia Monograph Compendial Name				Route of Administration	
Carbopol® Polymers	Residual Solvent	Polymer Type	Crosslinker	United States (USP/NF) Current	United States (USP/NF) Previous	Europe (Ph. Eur.)	Japan (JPE)[1]	Oral	Topical
971P NF	Ethyl acetate	Homopolymer	APE	Carbomer Homopolymer Type A	Carbomer 941	Carbomers[2]	Carboxyvinyl Polymer	•	•
71G NF	Ethyl acetate	Homopolymer	APE	Carbomer Homopolymer Type A	Carbomer 941	Carbomers[2]	Carboxyvinyl Polymer	•	•
974P NF	Ethyl acetate	Homopolymer	APE	Carbomer Homopolymer Type B	Carbomer 934P	Carbomers[2]	Carboxyvinyl Polymer	•	•
5984 EP	Cosolvent[3]	Homopolymer	AS	Carbomer Homopolymer Type B	Carbomer 934	Carbomers[2]	Carboxyvinyl Polymer		•
980 NF	Cosolvent	Homopolymer	APE	Carbomer Homopolymer Type C	Carbomer 940	Carbomers[2]	Carboxyvinyl Polymer		•
981 NF	Cosolvent	Homopolymer	APE	Carbomer Homopolymer Type A	Carbomer 941	Carbomers[2]	Carboxyvinyl Polymer		•
Ultrez 10 NF	Cosolvent	Interpolymer	AS	Carbomer Interpolymer Type A					•
ETD 2020 NF	Cosolvent	Interpolymer	APE	Carbomer Interpolymer Type B					•
934 NF[4]	Benzene	Homopolymer	AS	Carbomer 934	Carbomer 934		Carboxyvinyl Polymer		•
934P NF	Benzene	Homopolymer	AS	Carbomer 934P	Carbomer 934P		Carboxyvinyl Polymer	•	•
940 NF	Benzene	Homopolymer	APE	Carbomer 940	Carbomer 940		Carboxyvinyl Polymer		•
941 NF	Benzene	Homopolymer	APE	Carbomer 941	Carbomer 941		Carboxyvinyl Polymer		•
1342 NF	Benzene	Copolymer	APE	Carbomer 1342	Carbomer 1342		Carboxyvinyl Polymer		•

taste masking

residual Benzene 2 ppm

Benzene content 5000 ppm

[1] Based on customer request, Lubrizol certifies select lots of product against the JPE Carboxyvinyl Polymer Monograph.
[2] The Carbomers Monograph in the European Pharmacopeia stipulates that benzene is limited to 2 ppm.
[3] Cosolvent is a mixture of ethyl acetate and cyclohexane.
[4] Carbopol® 934 NF, 934P NF, 940 NF, 941 NF and 1342 NF polymers are not recommended for new product development due to regulatory restrictions on benzene.

APE = Allyl ethers of pentaerythritol
AS = Allyl ethers of sucrose

Cosolvent use combination of ethyl acetate & Cyclohexane.
941, 981, 971 Crosslinked polymer, low viscosity.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Product Type And Regulatory Status *(Cont'd)*

Polymer Chemistry				Pharmacopoeia Monograph Compendial Name			Route of Administration	
	Residual Solvent	Polymer Type	Crosslinker	United States (USP/NF)	Europe (Ph. Eur.)	Japan (JPE)	Oral	Topical
Pemulen™ Polymers								
TR-1 NF	Cosolvent	Copolymer	APE	Carbomer Copolymer Type B				•
TR-2 NF	Cosolvent	Copolymer	APE	Carbomer Copolymer Type A				•
Noveon® Polycarbophil								
AA-1 USP	Ethyl Acetate	Homopolymer	DVG	Polycarbophil			•	•

[1] Based on customer request, Lubrizol certifies select lots of product against the JPE Carboxyvinyl Polymer Monograph.
[2] The Carbomers Monograph in the European Pharmacopeia stipulates that benzene is limited to 2 ppm.
[3] Cosolvent is a mixture of ethyl acetate and cyclohexane.
[4] Carbopol® 934 NF, 934P NF, 940 NF, 941 NF and 1342 NF polymers are not recommended for new product development due to regulatory restrictions on benzene.

APE = Allyl ethers of pentaerythritol
DVG = Divinyl Glycol

940, 980 → high viscosity polymer.
ETD → easy to dispense.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Classification Based on Markets Served

Personal Care Grades

- Not tested to any compendial specifications
- Not Manufactured and tested according to cGMP requirements and compendial specifications.
- e.g Carbopol® 980
  Carbopol® 981
  Carbopol® Ultrez 10
  Pemulen® TR-1
  Pemulen® TR-2.
  Carbopol® 934
  Carbopol® 940
  Carbopol® 941
  etc.

Pharmaceutical Grades

- Meets compendial requirements (USP/NF, Ph. Eur.)
- Manufactured under cGMP conditions in Calvert City USA or Kallo Belgium.

e. g. Carbopol® 971P NF
Carbopol® 974P NF
Carbopol® 71G NF
Noveon® AA-1 (Polycarbophil USP)
Carbopol® 980 NF
Carbopol® 981 NF
Carbopol® Ultrez 10 NF
Pemulen® TR-1 NF
Pemulen® TR-2 NF
Carbopol® 934P NF
Carbopol® 934 NF
Carbopol® 940 NF
Carbopol® 941 NF
etc.

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Polymers | Formulation | Manufacturing

Choice of Polymer: Alternative Grades

Benzene Grade Carbopol® Polymer	Recommended Non-Benzene Carbopol® or Pemulen™ Polymers
Carbopol® 934 NF polymer	Carbopol® 5984 EP, 980 NF, ETD 2020 NF and Ultrez 10 NF polymers
Carbopol® 934P NF polymer	Carbopol® 974P NF polymer
Carbopol® 940 NF polymer	Carbopol® 980 NF and Ultrez 10 NF polymers
Carbopol® 941 NF polymer	Carbopol® 971P NF and 981 NF polymers
Carbopol® 1342 NF polymer	Pemulen™ TR-1 and TR-2 NF polymers

- Substitute products are polymerized in either ethyl acetate or a cosolvent mixture of ethyl acetate and cyclohexane.
- Key performance properties should be ascertained and regulatory considerations be taken into account when a substitution is made in a pharmaceutical formulation.
- Depending on the desired dosage requirements, other Carbopol® polymers may be suitable alternatives.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Inactive Ingredients Database Entries for Carbomer

Carbopol® and Polycarbophil polymers are represented by various names in IIG **PRIOR TO JULY 31, 2015** and they are as follows

- Carbomer 941, Carbomer 981
- Carbomer 934, Carbomer 934P, Carbomer 974
- Carbomer 940, carbomer 980
- Carbomer 1342
- Carbomer 1382
- Carboxypolymethylene, Polycarbophil and Calcium Polycarbophil

Carbopol® and Polycarbophil polymers are represented by various names in **IIG FROM 01 AUGUST 2015** and they are as follows

- Carbomer Homopolymer Type A
- Carbomer Homopolymer Type B
- Carbomer Homopolymer Type C
- Carbomer Copolymer Type B
- Carbomer 1382
- Carboxypolymethylene , Calcium Polycarbophil, Polycarbophil

Substance registration system.

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Polymers | Formulation | Manufacturing

Important IID entries for Carbomer Polycarbophil and Carboxypolymethylene

INACTIVE INGREDIENT	ROUTE	DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
CARBOMER 1382	TOPICAL	GEL	146701613	Pending	0.9 % W/W
CARBOMER COPOLYMER TYPE A (APE CROSSLINKED)	OPHTHALMIC	EMULSION	145687021	71DD5V995L	0.05% W/W
CARBOMER COPOLYMER TYPE B (APE CROSSLINKED)	TOPICAL	GEL	96827246	809Y72KV36	0.8% W/W
CARBOMER HOMOPOLYMER TYPE A (APE CROSSLINKED)	ORAL	TABLET, EXTENDED RELEASE	138757683	F68VH75CJC	175 MG
CARBOMER HOMOPOLYMER TYPE A (APE CROSSLINKED)	TOPICAL	GEL	138757683	F68VH75CJC	0.85 % W/W
CARBOMER HOMOPOLYMER TYPE B (APE CROSSLINKED)	ORAL	GRANULE, FOR SUSPENSION	151687966	HHT01ZNK31	150 MG
CARBOMER HOMOPOLYMER TYPE B (APE CROSSLINKED)	ORAL	GEL	151687966	HHT01ZNK31	1.25 % W/W
CARBOMER HOMOPOLYMER TYPE B (APE CROSSLINKED)	TOPICAL	CREAM	151687966	HHT01ZNK31	1.2 % W/W

- SRS.com (data base) for chemical names.
- dailymed.com
- IPECamericas.com for excipients.

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Polymers | Formulation | Manufacturing

Important IID entries for Carbomer Polycarbophil and Carboxypolymethylene

INACTIVE INGREDIENT	ROUTE	DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
CARBOMER HOMOPOLYMER TYPE B (APE OR AS CROSSLINKED)	ORAL	TABLET, SUSTAINED ACTION	57916924	K6MOM3T5YL	90 MG
CARBOMER HOMOPOLYMER TYPE B (APE OR AS CROSSLINKED)	OPHTHALMIC	SUSPENSION	57916924	K6MOM3T5YL	0.4 %
CARBOMER HOMOPOLYMER TYPE B (APE OR AS CROSSLINKED)	TOPICAL	GEL	57916924	K6MOM3T5YL	1.51% W/W
CARBOMER HOMOPOLYMER TYPE B (APE OR AS CROSSLINKED)	VAGINAL	GEL	57916924	K6MOM3T5YL	2% W/W
CARBOMER HOMOPOLYMER TYPE C (APE CROSSLINKED)	OPHTHALMIC	GEL	57916924	4Q93RCW27E	4 %
CARBOMER HOMOPOLYMER TYPE C (APE CROSSLINKED)	TOPICAL	GEL	57916924	4Q93RCW27E	3.5% W/W

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Polymers | Formulation | Manufacturing

Important IID entries for Carbomer Polycarbophil and Carboxypolymethylene

INACTIVE INGREDIENT	ROUTE	DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TRANSDERMAL	GEL	57916924	4Q93RCW27E	1.5 %
POLYCARBOPHIL	BUCCAL	TABLET	9003978	W25LM17A4W	3.13 MG
POLYCARBOPHIL	OPHTHALMIC	SOLUTION	9003978	W25LM17A4W	0.9 %
POLYCARBOPHIL	TOPICAL	SOLUTION	9003978	W25LM17A4W	0.88 % W/W
POLYCARBOPHIL	VAGINAL	GEL	9003978	W25LM17A4W	2.25 %
CARBOXYPOLYMETHYLENE	ORAL	TABLET, SUSTAINED ACTION	9003014	0A5MM307FC	195 MG/day dose

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Regulatory Support for NDA/ANDA

- Lubrizol has established a Type V DMF (# 26860) titled "*Toxicology and Regulatory Review – Carbomer Class of Polymers*" with FDA
  - The DMF includes bridging data justifying the maximum precedence of use level and ADI for carbomer homopolymers
  - Toxicological equivalence is based on chemical composition (crosslinked polyacrylic acid), molecular weight, lack of bioavailability and inability to be metabolized, solvent systems and residual impurities
  - Full toxicology study reports are also included in the DMF.
- Lubrizol can provide letters of access (LOA) for the above DMF including reference to specific page numbers in the DMFs which contain pharmacology and toxicology information
- The bridging arguments and information included in this DMF should facilitate FDA review of excipient information as part of the drug application

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Lubrizol LifeSciences Regulatory Data on Website

- The website can be accessed by the link http://www.lubrizol.com/Pharmaceutical/default.html
- The following documents are available freely on the website
- MSDS,
- Specifications,
- IID and USP NF status of Pharma Polymers
- Product allergen statements
- ISO certificates for Calvert city USA and Kallo Belgium manufacturing plants
- BSE TSE and Kosher Certificates
- Technical Data Sheets on several topics including Toxicological information

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Excipient Information Package (EIP) Documents

- Excipient Information Package (EIP) documents follow the format and guidelines established and recommended by the International Pharmaceutical Excipients Council (IPEC).
- These documents cover all the vendor qualification regulatory requirements of global customers and comprise of the following documents
- EIP regulatory Data sheet Final
- EIP package site quality overview Calvert City Pharma
- EIP package site and supply chain security overview Calvert City
- EIP package site quality overview Carbopol 71G NF
- EIP package site and supply chain security overview Carbopol 71G NF

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Polymers | Formulation | Manufacturing

Carbomer Requirements for Pharmacopeial Compliance

Requirement (Standard)	Specific monograph *Carbomer Homopolymer Carbomer Copolymer Carbomer Interpolymer*
Identification	Y
Assay - Content of Carboxylic Acid	Y
Residue on Ignition	Y
Limit of Ethyl Acetate and Cyclohexane	Y
Limit of Benzene	Y
Limit of Acrylic Acid	Y
Loss on Drying	Y
Viscosity—Rotational Methods	Y

Compliance to USP requires conformance to standards from the relevant monograph, general chapters, and general notices

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Carbomer Effect on Pharmacopeial Compliance of Drug Products

Requirement (Standard)	Specific monograph *Carbomer Homopolymer* *Carbomer Copolymer* *Carbomer Interpolymer*	General Chapters Requirement Applicable to Drug Products
Residual Solvents		<467>
Elemental Impurities*		<232>, <233>

** Implementation starting Jan 2018. Till then Heavy Metals <231> applicable.*

Information on excipients residual solvents and elemental impurities is important for risk evaluation and management of those limits in drug product(s)

Lubrizol

Carbopol® Polymers - Composition Profile Specifications

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Carbopol® Polymers for Oral Delivery – Carbomer Homopolymers - Specifications

Characteristic	Compendial Specification USP/NF Carbomer Homopolymer	Lubrizol Specification Carbopol 971P NF, 974P NF and 71G NF Polymer
Limit of Ethyl Acetate (%)	0.5 max	0.5 max
Limit of Cyclohexane (%)	0.3 max	Not used in manufacturing process of products designed for oral delivery
Limit of Benzene (ppm)	2.0 max	0.5 max Benzene is tested due to it being a potential impurity.
Limit of Acrylic Acid (%)	0.25 max	0.10 max
Residual Solvents	USP <467> Ph. Eur. 2.4.24	No other residual solvents as listed in USP/NF <467> (Class 1, 2, 3, Table 4 or any other solvents) or Ph. Eur. 2.4.24 are used in the manufacturing process of this product.

Carbopol® polymer product specifications are the same as or stricter than pharmacopeial requirements

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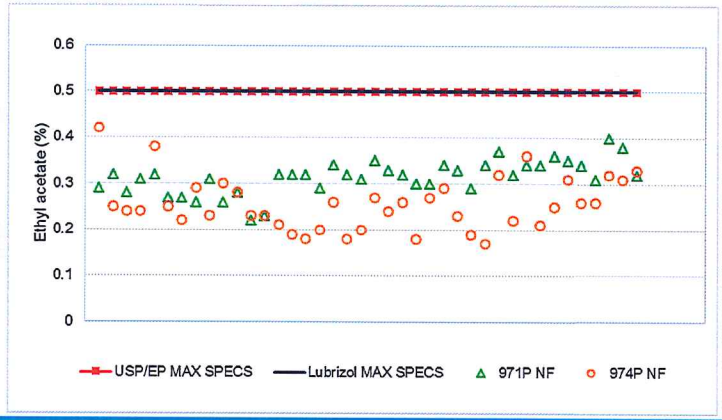
Polymers | Formulation | Manufacturing

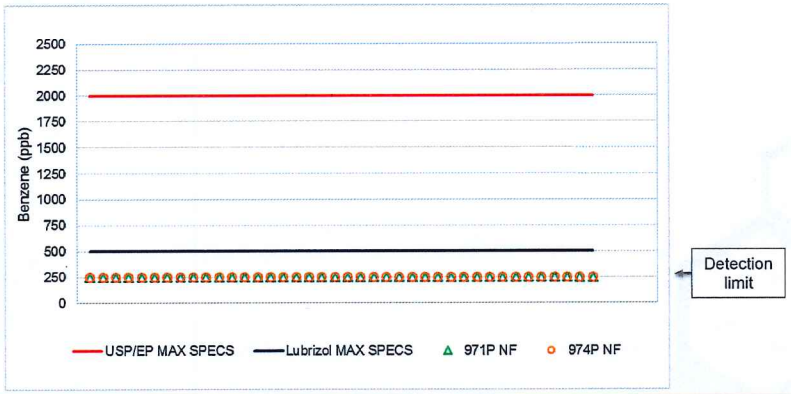
Carbopol® Polymers for Oral Drug Delivery – Specifications and Values



Residual ethyl acetate content has been well below the pharmacopeial monograph and product specification (NMT 0.5%)

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Carbopol® Polymers for Oral Drug Delivery – Specifications and Values



Residual benzene is tested due to it being a potential impurity. Lubrizol specifications are much lower than pharmacopeial monograph limit, and actual benzene values are below the limit of detection for our polymers recommended for oral drug delivery

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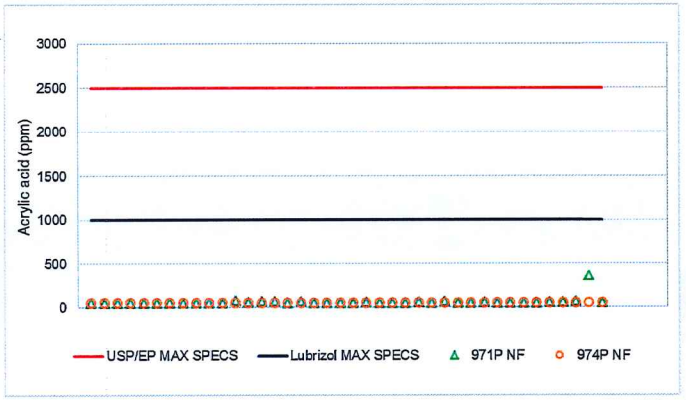
Carbopol® Polymers for Oral Drug Delivery – Specifications and Values



The Carbopol® product specification for residual acrylic acid is significantly lower than the pharmacopeial limit. Acrylic acid values have historically been significantly lower than Lubrizol's specification

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

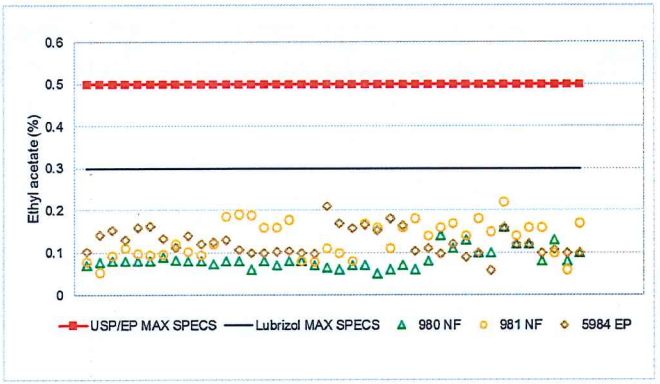
Carbopol® Polymers for Topical Administration – Carbomer Homopolymers - Specifications

Characteristic	Compendial Specification USP/NF Carbomer Homopolymer EP Carbomers	Lubrizol Specification Carbopol 981 NF, 980 NF and 5984 EP Polymer
Limit of Ethyl Acetate (%)	0.5 max	0.3 max
Limit of Cyclohexane (%)	0.3 max	0.3 max
Limit of Benzene (ppm)	2.0 max	0.5 max Benzene is tested due to it being a potential impurity.
Limit of Acrylic Acid (%)	0.25 max	0.25 max
Residual Solvents	USP <467> Ph. Eur. 2.4.24	No other residual solvents as listed in USP/NF <467> (Class 1, 2, 3, Table 4 or any other solvents) or Ph. Eur. 2.4.24 are used in the manufacturing process of this product.

Carbopol® polymer product specifications are similar or stricter than pharmacopeial requirements

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

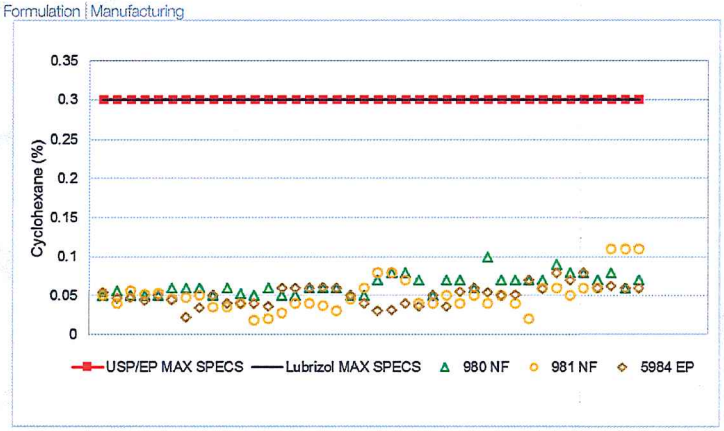
Carbopol® Polymers for Topical Delivery – Carbomer Homopolymers Specifications and Values



Residual ethyl acetate content has been well below the pharmacopeial monograph (NMT 0.5%) and Lubrizol's product specification (NMT 0.3%)

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

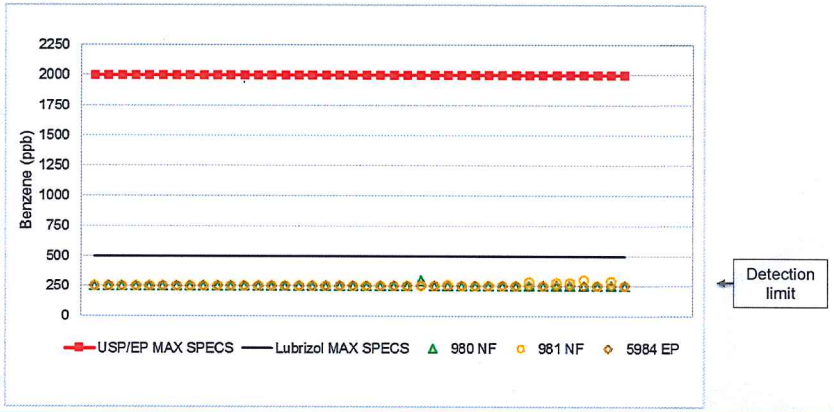
Carbopol® Polymers for Topical Delivery – Carbomer Homopolymers Specifications and Values



Residual cyclohexane content has been well below the pharmacopeial monograph and product specification (NMT 0.3%)

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Carbopol® Polymers for Topical Delivery – Carbomer Homopolymers Specifications and Values



Benzene is tested due to it being a potential impurity. Lubrizol's specification is much lower than pharmacopeial monograph limit. Benzene values have historically been very low or below our detection limit of 250 ppb

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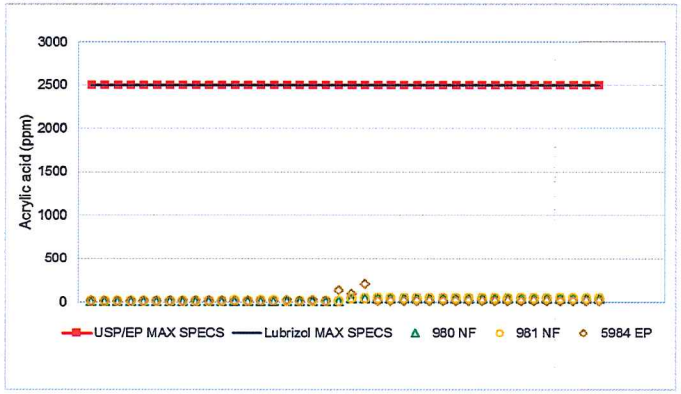
Polymers | Formulation | Manufacturing

Carbopol® Polymers for Topical Delivery – Carbomer Homopolymers Specifications and Values



Residual acrylic acid values have historically been much lower than the pharmacopeial limit and Lubrizol's product specification (NMT 2500 ppm)

Lubrizol

Carbopol® Polymers vs. Carbomers

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Pharmacopeial Considerations: Carbopol® Polymers vs Carbomers

Pharmacopeia	Carbopol Polymers Pemulen Polymers Noveon Polycarbophil	Other carbomers
Requirements pharmacopeial specific monograph • *Carbomer homopolymer* • *Carbomer copolymer* • *Carbomer interpolymer*	✓	✓
Residual Solvents* (General chapters)	Ethyl acetate or mixture of ethyl acetate and cyclohexane No other residual solvents as listed in USP/NF <467> (Class 1, 2, 3, Table 4 or any other solvents) or Ph. Eur. 2.4.24 used in the manufacturing process. Benzene is tested due to it being a potential impurity.	Various solvents/co-solvents: • Benzene (class I) • 1,2-dichloroethane (class I) • Methylene chloride (class II) • Ethyl acetate – cyclohexane, etc *Some solvents not listed in carbomer monographs* **Recommended to identify and measure residual solvents even when test is not listed in the specific carbomer monograph (USP-NF <467> and EP 5.4).**
Elemental Impurities* (General chapters)	Excipients have been tested for elemental impurities following ICH Q3D guidelines. Data is available to customers to ensure compliance of their drug product	TBE

** Applicable to drug products. Information on excipients residual solvents and elemental impurities is important for risk evaluation and management of those limits in drug product(s).*

Lubrizol LifeSciences
Polymers Formulation Manufacturing

SUMMARY - Carbopol® Polymers

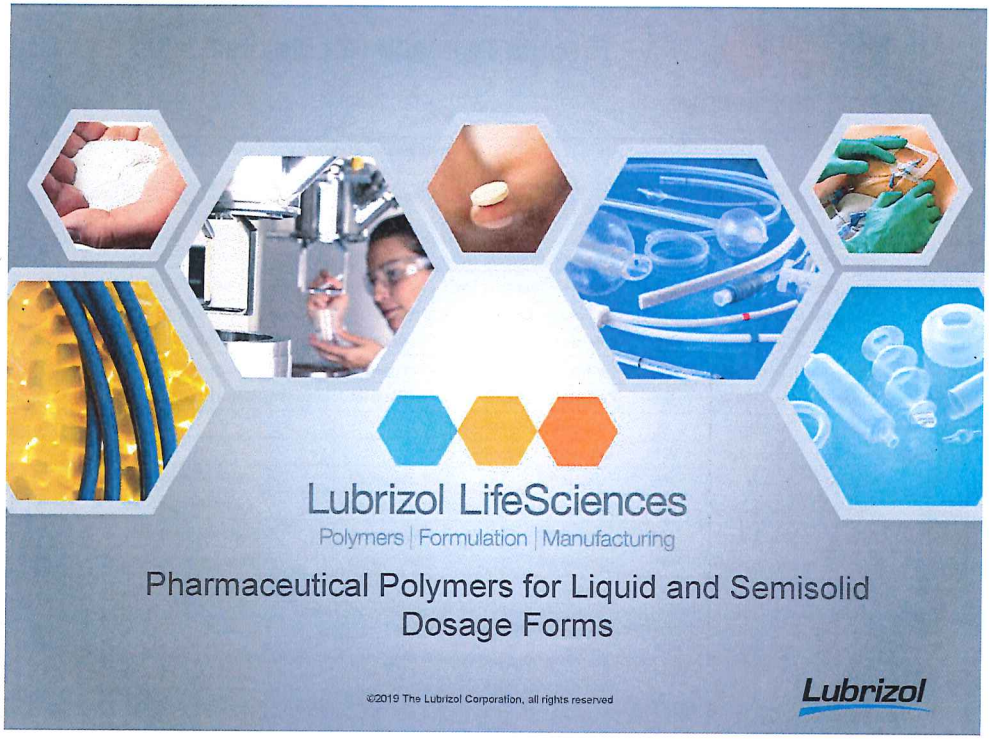
- Compendial compliance
- Quality
- Total Excipient Control

Patient Safety is Key for Lubrizol

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Total Excipient Control: Carbopol® Polymers vs Carbomers

Total Excipient Control	Carbopol Polymers Pemulen Polymers Noveon Polycarbophil	Other carbomers
Excipient Design	➢ Availability of COA, EIP, QA and regulatory support (FDA IID, QbD etc.) ➢ Stability evaluation and assessment	
Excipient Safety	➢ Toxicology/safety data on excipients and bridging arguments to help higher usage level of excipients	
Excipient Manufacturing Process Control and Distribution	➢ Excipients manufactured under GMP ➢ Management of significant change ➢ Ensure excipient pedigree including good supplier practices	



Lubrizol

Overview - Carbopol® and Pemulen™ Polymers, Noveon® Polycarbophil

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Outline

- Carbopol® and Pemulen™ Polymers, Noveon® Polycarbophil
  - Chemistry and description
  - Product type and regulatory status
  - Supply position for Pharmaceutical grades
- Polymer functionality
  - Thickening with a wide range of flow properties
  - Suspension stabilization
  - Emulsion Stabilization
- Formulation and processing considerations
  - Formulation ingredients
  - Dispersion preparation / pH adjustment
  - General recommendations
  - Equipment cleaning
- Stability and handling
- Commercial products – dosage forms / administration routes

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Polymers | Formulation | Manufacturing

Pharmaceutical Grade Polymers – Chemical Description

Product Types	Description
Carbomer Homopolymers	Polymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythritol
Carbomer Copolymers	Polymers of acrylic acid and a C10 – C30 alkyl acrylate crosslinked with allyl pentaerythritol
Carbomer Interpolymers	Carbomer homopolymers or copolymers that contain a block copolymer of polyethylene glycol and a long chain alkyl acid ester
Polycarbophil	Polymer of acrylic acid crosslinked with divinyl glycol

All Lubrizol products are high molecular weight, crosslinked, acrylic acid-based polymers

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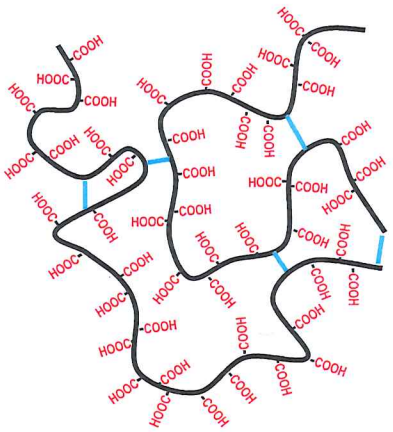
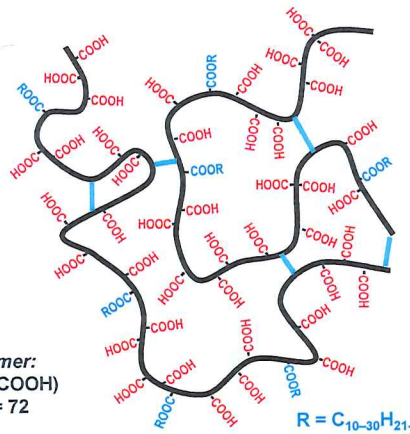
Polymers | Formulation | Manufacturing

Lubrizol Pharmaceutical Polymers

Carbomer Homopolymers



Carbomer Copolymers



Monomer:
CH_2CH (COOH)
MW = 72

R = $C_{10-30}H_{21-61}$

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Polymers | Formulation | Manufacturing

Product Type and Regulatory Status

				Pharmacopoeia Monograph Compendial Name				Route of Administration	
Carbopol® Polymers	Residual Solvent	Polymer Type	Crosslinker	United States (USP/NF) Current	United States (USP/NF) Previous	Europe (Ph. Eur.)	Japan (JPE)[1]	Oral	Topical
971P NF	Ethyl acetate	Homopolymer	APE	Carbomer Homopolymer Type A	Carbomer 941	Carbomers[2]	Carboxyvinyl Polymer	•	•
71G NF	Ethyl acetate	Homopolymer	APE	Carbomer Homopolymer Type A	Carbomer 941	Carbomers[2]	Carboxyvinyl Polymer	•	•
974P NF	Ethyl acetate	Homopolymer	APE	Carbomer Homopolymer Type B	Carbomer 934P	Carbomers[2]	Carboxyvinyl Polymer	•	•
5984 EP	Cosolvent[3]	Homopolymer	AS	Carbomer Homopolymer Type B	Carbomer 934	Carbomers[2]	Carboxyvinyl Polymer		•
980 NF	Cosolvent	Homopolymer	APE	Carbomer Homopolymer Type C	Carbomer 940	Carbomers[2]	Carboxyvinyl Polymer		•
981 NF	Cosolvent	Homopolymer	APE	Carbomer Homopolymer Type A	Carbomer 941	Carbomers[2]	Carboxyvinyl Polymer		•
Ultrez 10 NF	Cosolvent	Interpolymer	AS	Carbomer Interpolymer Type A					•
ETD 2020 NF	Cosolvent	Interpolymer	APE	Carbomer Interpolymer Type B					•
934 NF[4]	Benzene	Homopolymer	AS	Carbomer 934	Carbomer 934		Carboxyvinyl Polymer		•
934P NF	Benzene	Homopolymer	AS	Carbomer 934P	Carbomer 934P		Carboxyvinyl Polymer	•	•
940 NF	Benzene	Homopolymer	APE	Carbomer 940	Carbomer 940		Carboxyvinyl Polymer		•
941 NF	Benzene	Homopolymer	APE	Carbomer 941	Carbomer 941		Carboxyvinyl Polymer		•
1342 NF	Benzene	Copolymer	APE	Carbomer 1342	Carbomer 1342		Carboxyvinyl Polymer		•

[1] Based on customer request, Lubrizol certifies select lots of product against the JPE Carboxyvinyl Polymer Monograph.
[2] The Carbomers Monograph in the European Pharmacopeia stipulates that benzene is limited to 2 ppm.
[3] Cosolvent is a mixture of ethyl acetate and cosolvent.
[4] Carbopol® 934 NF, 934P NF, 940 NF, 941 NF and 1342 NF polymers are not recommended for new product development due to regulatory restrictions on benzene.

APE = Allyl ethers of pentaerythritol
AS = Allyl ethers of sucrose

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Product Type and Regulatory Status (Cont'd)

				Pharmacopoeia Monograph Compendial Name			Route of Administration	
	Residual Solvent	Polymer Type	Crosslinker	United States (USP/NF)	Europe (Ph. Eur.)	Japan (JPE)	Oral	Topical
Pemulen™ Polymers								
TR-1 NF	Cosolvent	Copolymer	APE	Carbomer Copolymer Type B				•
TR-2 NF	Cosolvent	Copolymer	APE	Carbomer Copolymer Type A				•
Noveon® Polycarbophil								
AA-1 USP	Ethyl Acetate	Homopolymer	DVG	Polycarbophil			•	•

APE = Allyl ethers of pentaerythritol
DVG = Divinyl Glycol

[1] Based on customer request, Lubrizol certifies select lots of product against the JPE Carboxyvinyl Polymer Monograph.
[2] The Carbomers Monograph in the European Pharmacopeia stipulates that benzene is limited to 2 ppm.
[3] Cosolvent is a mixture of ethyl acetate and cosolvent.
[4] Carbopol® 934 NF, 934P NF, 940 NF, 941 NF and 1342 NF polymers are not recommended for new product development due to regulatory restrictions on benzene.

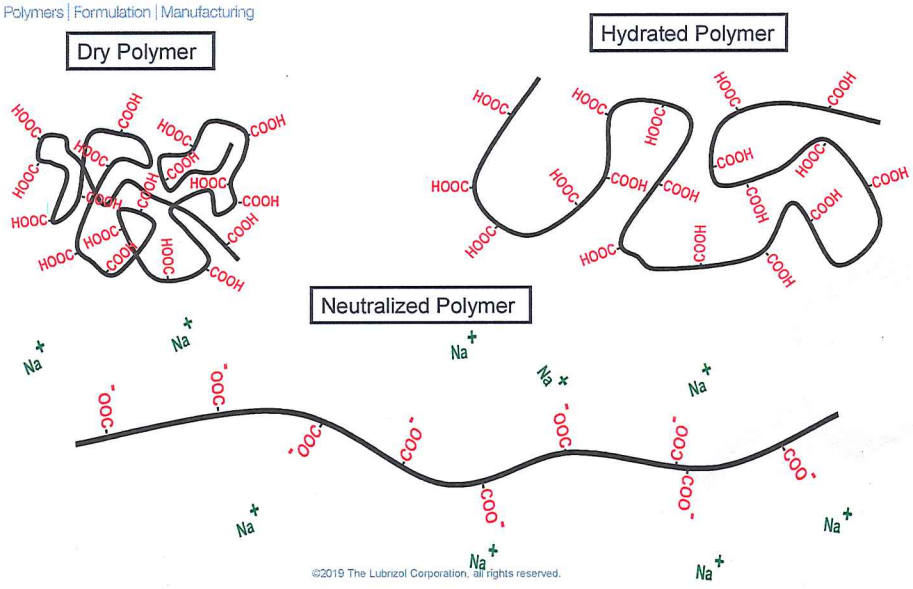
Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Typical Polymer Usage Levels

Application	Usage Level (wt. %)
Topical aqueous gel	0.5 – 3.0
Topical hydroalcoholic gel	0.5 – 3.0
Topical emulsions	0.1 – 0.4
Oral suspension / solution	0.1 – 1.0

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Carbopol® Polymers Swelling Mechanism



dispersion in room temp. water for 45 min to 1 hr.

hydration up to 2% polymer 98% water

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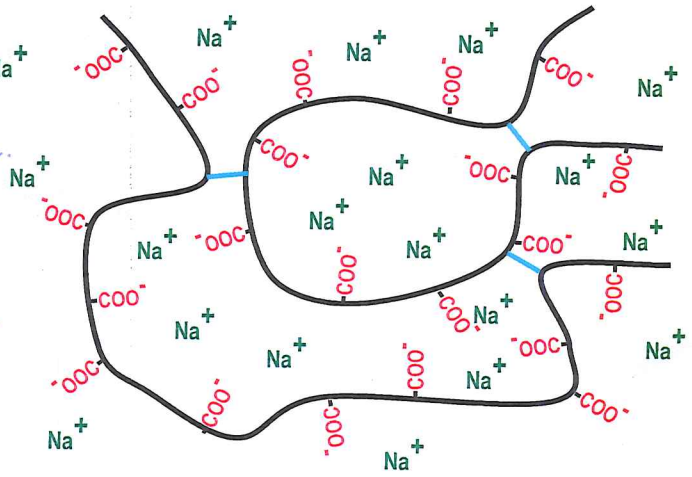
Polymers | Formulation | Manufacturing

Carbopol® Polymers Swelling Mechanism (Cont'd)



→ Water Swellable but not Water Soluble.

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Polymers | Formulation | Manufacturing

Carbopol® Polymers – Swelling and Thickening

Dilute
- Particles are swollen to equilibrium
- ($c < c^*$)

low viscosity

Transition
- Particles are swollen to equilibrium
- ($c = c^*$)

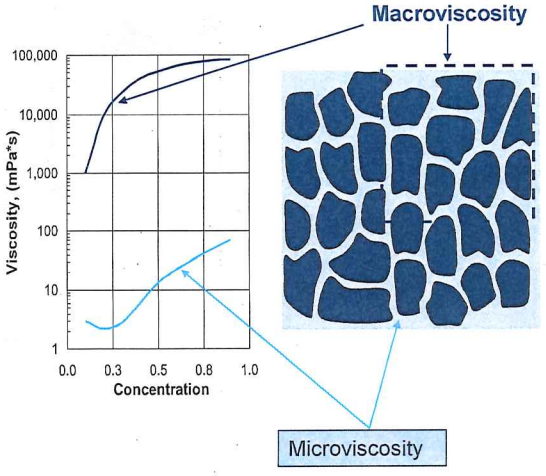
Concentrated
- Particles are swollen to less than equilibrium
- ($c > c^*$)

c: concentration of dispersion of Carbopol® polymer
c*: critical overlap concentration

to achieve Best hydration and swelling the polymer should be fully uncoiled which is achieved using Base (NaOH) KOH to neutralize the Polymer.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Macroviscosity vs. Microviscosity



- ❑ Macroviscosity
  - As typically measured by Brookfield viscometer
- ❑ Microviscosity
  - Viscosity of the liquid in the interstitial spaces, between swollen gel particles.
  - Plastic rheology

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Polymers | Formulation | Manufacturing

Supply Position for Pharmaceutical Grade Products

cGMP Manufacturing Locations	Calvert City, KY (U.S.)	Antwerp (Kallo), Belgium
Solvent Platforms	- Benzene - Ethyl Acetate - Cosolvent	- Cosolvent
Products Produced	- Carbopol® Polymers - Pemulen™ Polymers - Noveon® AA-1 Polycarbophil	- Select Carbopol® Polymers - Select Pemulen™ Polymers

Products are offered through a global supply network of direct sales and distributors

Lubrizol

Polymer Functionality

Lubrizol

Thickening with a Wide Range of Flow Properties

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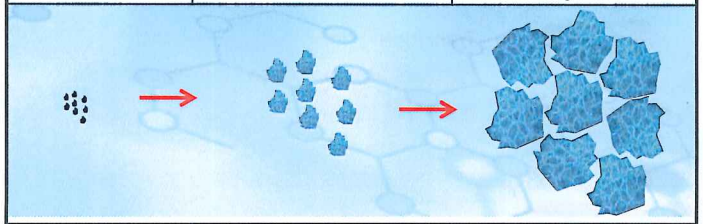
Polymers | Formulation | Manufacturing

Carbopol® Polymers - Swelling

Dry Polymer	Hydrated Polymer	Neutralized Polymer
		
Ø = 2 - 7µm	pH = 3.0	Ø = 20- 70µm pH = 7.0

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Polymers | Formulation | Manufacturing

Carbopol® Polymers – Swelling and Thickening

- Neutralization with bases (organic, inorganic, amino acids, etc) – **Major Mechanism**
- Hydrogen bonding

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Polymers | Formulation | Manufacturing

Viscosity of Carbopol® Polymers in Aqueous Dispersions

- Highly efficient thickeners, at low usage levels (0.1 - 3 wt. %).
- Viscosity of the dispersions increases with the polymer level.
- Viscosity increases at pH=4 and begins to decrease at pH=9 and higher.
- Maximum viscosity typically achieved at pH = 6.0 - 7.0 (pKa=6.0 ± 0.5).
- Addition of a neutralizer to aqueous dispersions of Carbopol® polymers results in gradual thickening.
- Higher levels of Carbopol® polymers enable reaching the maximum viscosity at lower pH values.
- Increased polymer concentrations are recommended for robust formulations at pH values below 5 and above 9.

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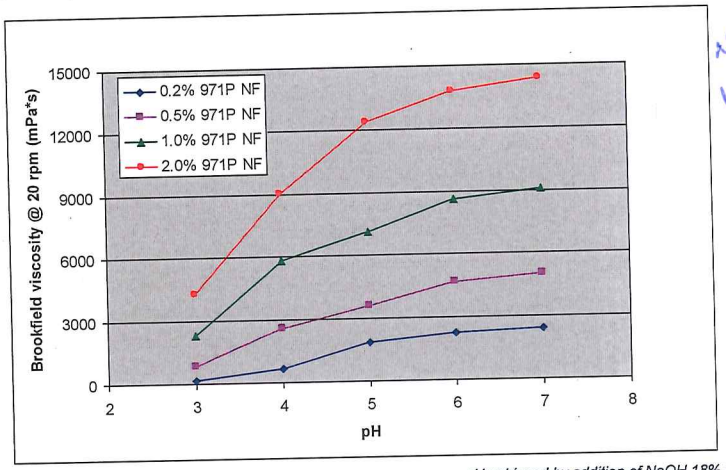
Polymers | Formulation | Manufacturing

Effect of pH and Concentration on the Viscosity of Carbopol® 971P NF Polymer Dispersion



No direct correlation between conc. & viscosity.

pH achieved by addition of NaOH 18% solution

Higher concentration leads to higher viscosity

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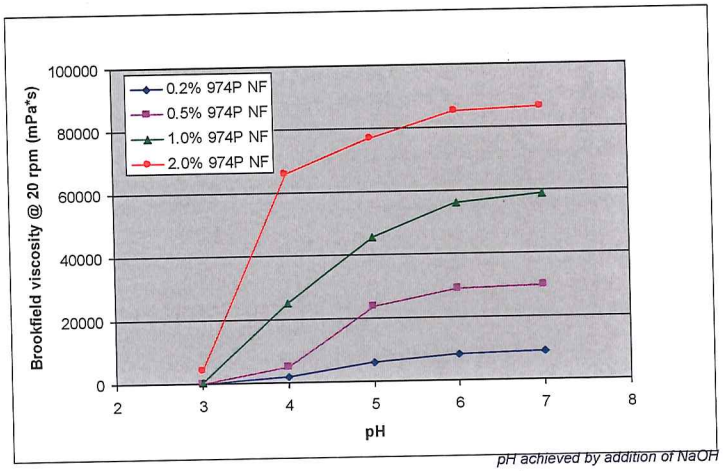
Polymers | Formulation | Manufacturing

Effect of pH and Concentration on the Viscosity of Carbopol® 974P NF Polymer Dispersion



pH achieved by addition of NaOH 18% solution

Higher concentration leads to higher viscosity

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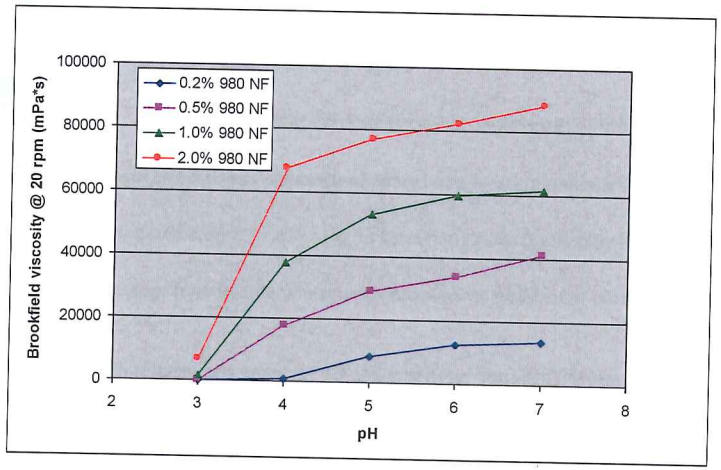
Polymers | Formulation | Manufacturing

Effect of pH and Concentration on the Viscosity of Carbopol® 980 NF Polymer Dispersion



pH achieved by addition of NaOH 18% solution

Higher concentration leads to higher viscosity

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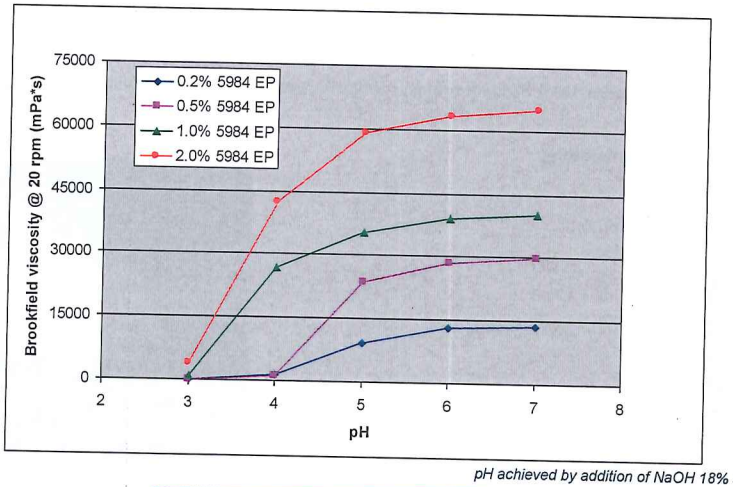
Polymers | Formulation | Manufacturing

Effect of pH and Concentration on the Viscosity of Carbopol® 5984 EP Polymer Dispersion



pH achieved by addition of NaOH 18% solution

Higher concentration leads to higher viscosity

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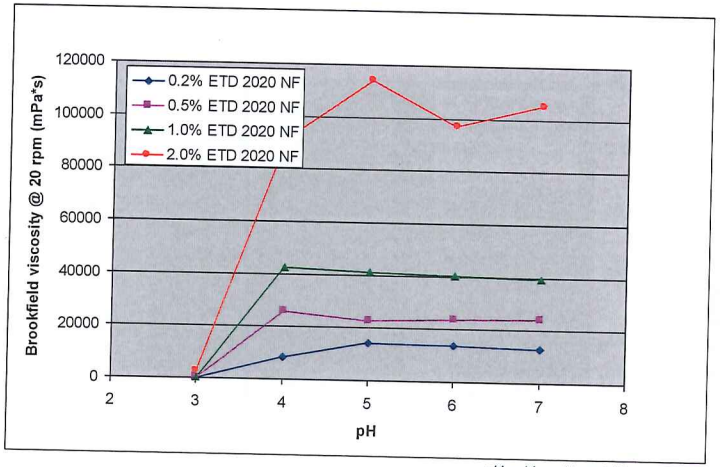
Polymers | Formulation | Manufacturing

Effect of pH and Concentration on the Viscosity of Carbopol® ETD 2020 NF Polymer Dispersion



pH achieved by addition of NaOH 18% solution

Higher concentration leads to higher viscosity

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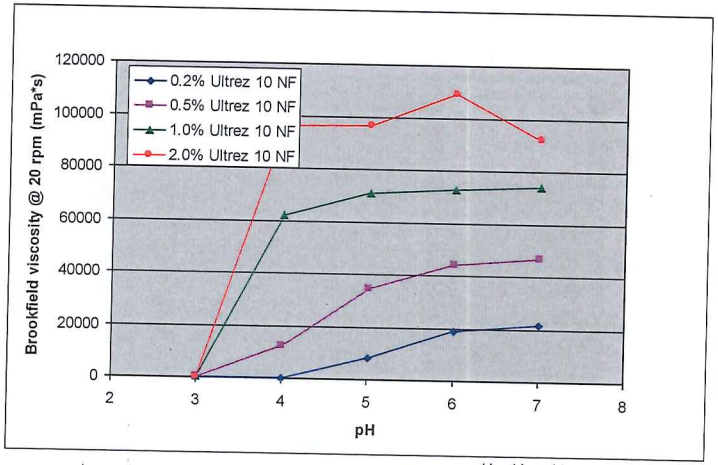
Polymers | Formulation | Manufacturing

Effect of pH and Concentration on the Viscosity of Carbopol® Ultrez 10 NF Dispersion



pH achieved by addition of NaOH 18% solution

Higher concentration leads to higher viscosity

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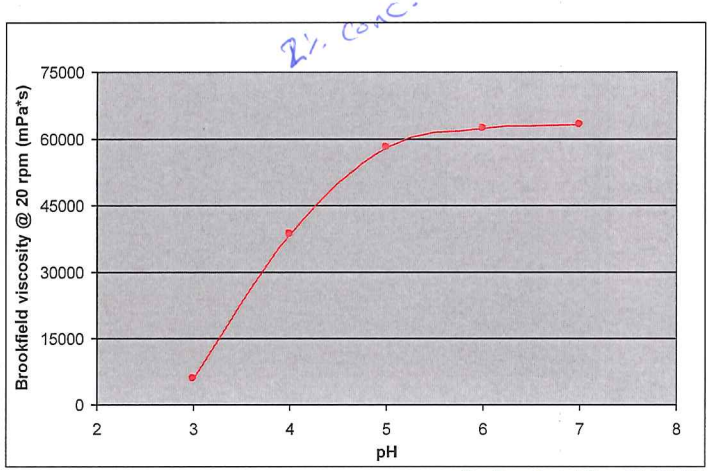
Polymers | Formulation | Manufacturing

Effect of pH on the Viscosity of Noveon® AA-1 Polycarbophil Dispersion (2.0%)



pH achieved by addition of NaOH 18% solution

Lightly crosslinked polymers plateau at lower pH

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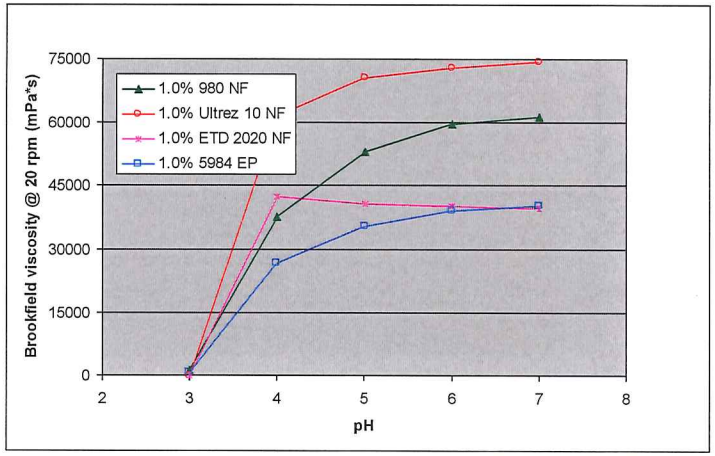
Polymers | Formulation | Manufacturing

Effect of Polymer Type on the Viscosity of 1.0% Dispersions – Topical Products



pH achieved by addition of NaOH 18% solution

Carbopol Ultrez 10 NF Polymer gives highest viscosity

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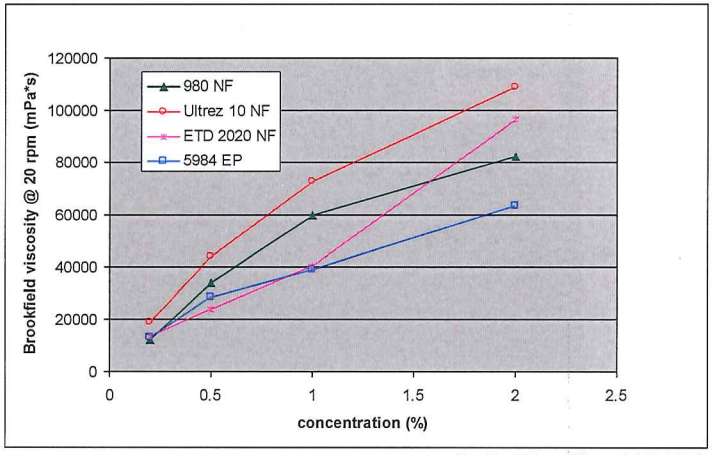
Polymers | Formulation | Manufacturing

Effect of Polymer Type and Concentration on the Viscosity at pH 6.0 – Topical Products



pH achieved by addition of NaOH 18% solution

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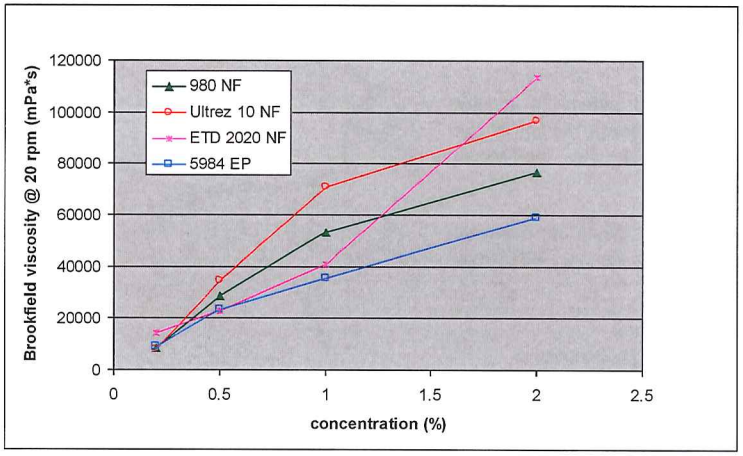
Polymers | Formulation | Manufacturing

Effect of Polymer Type and Concentration on the Viscosity at pH 5.0 – Topical Products



pH achieved by addition of NaOH 18% solution

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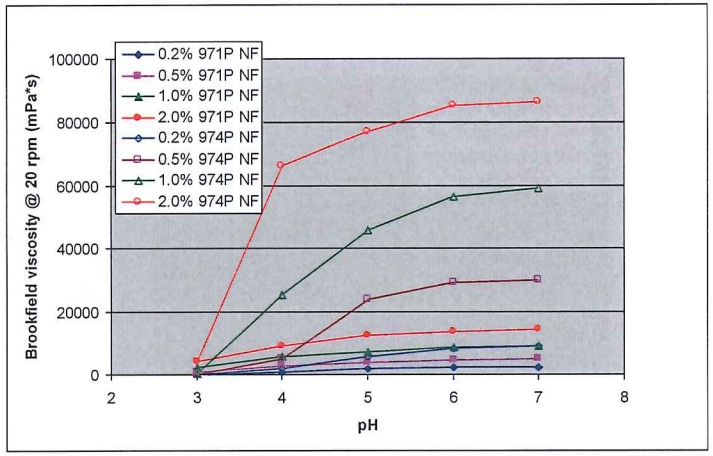
Polymers | Formulation | Manufacturing

Effect of pH and Concentration on the Viscosity of Carbopol® 971P NF and 974P NF Polymer Dispersions



971 has plateau at low pH.
- low crosslinked polymers swells at low pH
- high crosslinked swells at high pH.
- Ultrez doesn't swell in water.

pH achieved by addition of NaOH 18% solution

Lightly crosslinked Carbopol 971P plateaus at lower pH

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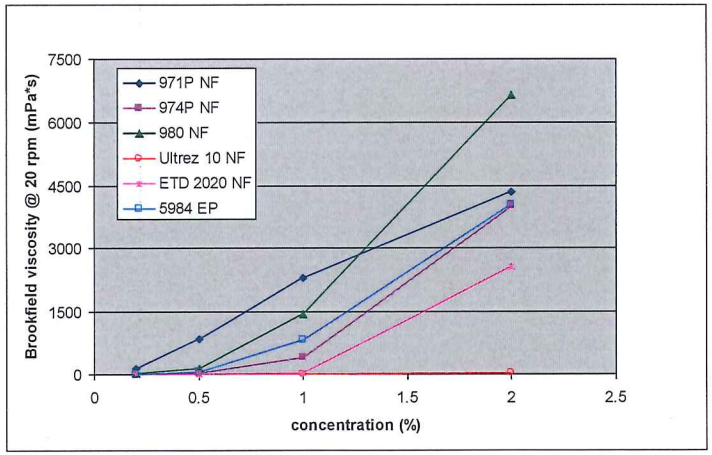
Polymers | Formulation | Manufacturing

Effect of Polymer Type and Concentration on the Viscosity of Dispersions as Prepared



Interpolymers have very low un-neutralized dispersion viscosity

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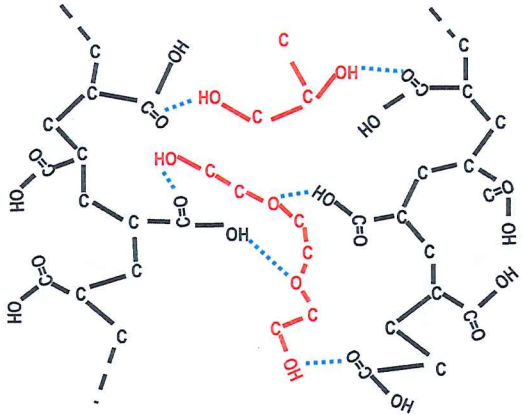
Polymers | Formulation | Manufacturing

Viscosity of Carbopol® Polymer Dispersions – Hydrogen Bonding using 40-50% of glycerin.

- Carbopol® polymers may form hydrogen bonds with co-excipients that are hydroxyl donors.
- Recommended when it is not feasible to increase the pH of the formulation or in anhydrous systems.
- Slow process - taking up to several hours; heating (up to 60°C) may accelerate it.
- Hydroxyl donors:
  - Polyols (glycerine, propylene glycol and polyethylene glycol)
  - Sugar alcohols (mannitol, sorbitol)
  - Some nonionic surfactants
  - Polyethylene oxide



* without neutralization.

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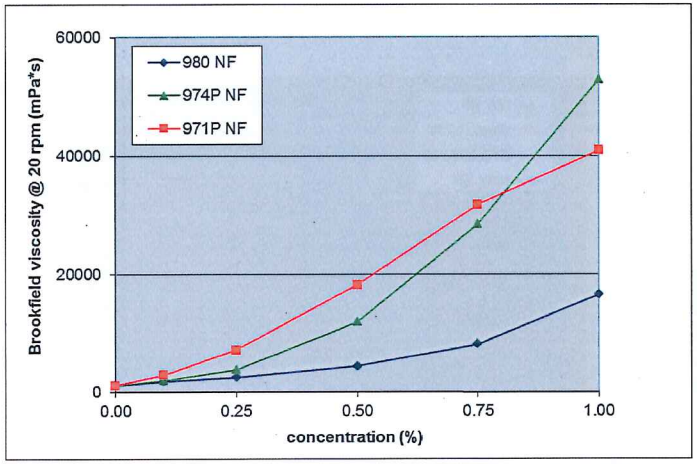
Viscosity of Carbopol® Polymer Dispersions in Glycerin – Hydrogen Bonding



No neutralizer added

Lightly crosslinked polymers give more viscosity than highly crosslinked

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Carbopol® Polymer Dispersions – Neutralizers

- Selection – determined by the vehicle and intended product characteristics.
- Amount – function of target pH; it may be calculated (using an equivalent weight of 76 for the Carbopol® polymer)
- Addition - under mild agitation

Hydroalcoholic systems (up to alcohol %)	Neutralizer
20 - 30	Sodium hydroxide or potassium hydroxide
60	Triethanolamine
60	Tromethamine
80	Aminomethyl propanol

approved for oral and ophthalmic.

Neutralizer / amount	Approx amount for one part polymer (pH=6-7)
Sodium hydroxide (18% solution)	2.30
Potassium hydroxide (18% solution)	3.30
Ammonium hydroxide (28%solution)	0.70
Triethanolamine	1.50
Tromethamine	1.30
Aminomethyl propanol	0.95

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Products Recommended for Topical Applications

Carbopol® and Pemulen™ Polymers for Liquid and Semisolid Applications					
Easy Dispersing or Self Wetting Polymers	Ultrez 10 NF				ETD 2020 NF
Ethyl Acetate Polymers		974P NF		971P NF	
Cosolvent Polymers		5984 EP	980 NF	981 NF	TR-1 & TR-2 NF[1]
Benzene Polymers		934 NF, 934P NF	940 NF	941 NF	1342 NF
Properties in a Formulated Application					
Relative Viscosity	High	High	High	Low	Low/Medium
Flow Characteristics	Short	Short	Short	Long	Long
Suspending Ability	High	High	High	High	High
Mucilage Clarity	High	Low	High	High	High
Relative Ion Tolerance	Low	Low	Medium	Medium	High
Applications					
Solutions/Suspension/Emulsions	●	●	●	●	●
Creams	●	●	●		●
Clear Gels	●	●	●	●	●
Hydroalcoholic Gels	●	●	●	●	●
Electrolyte Systems					●

Short Flow Long Flow

[1] Pemulen™ Polymers (Pemulen TR-1 NF and TR-2 NF). All other products noted in table belong to the Carbopol® polymer product family.

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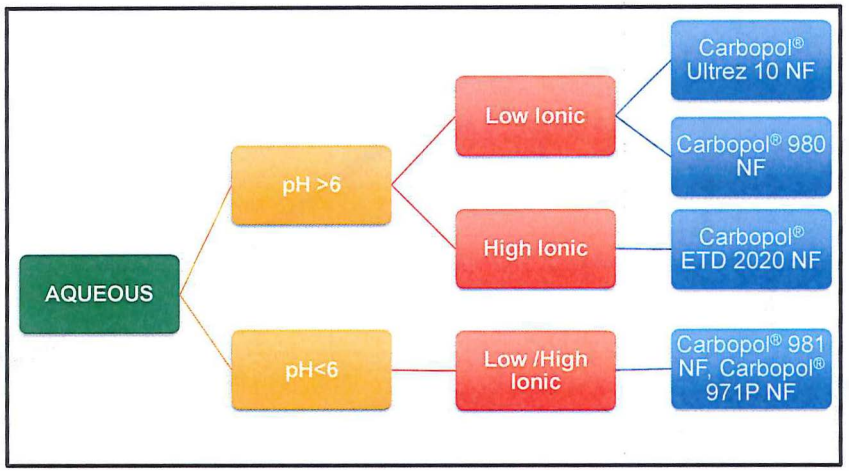
Polymer Selection - Aqueous Formulations



<4.5pH with KOH/NaOH the polymer will not fully swells. So glycerin is better to use. (hydrogen Bond mechanism.

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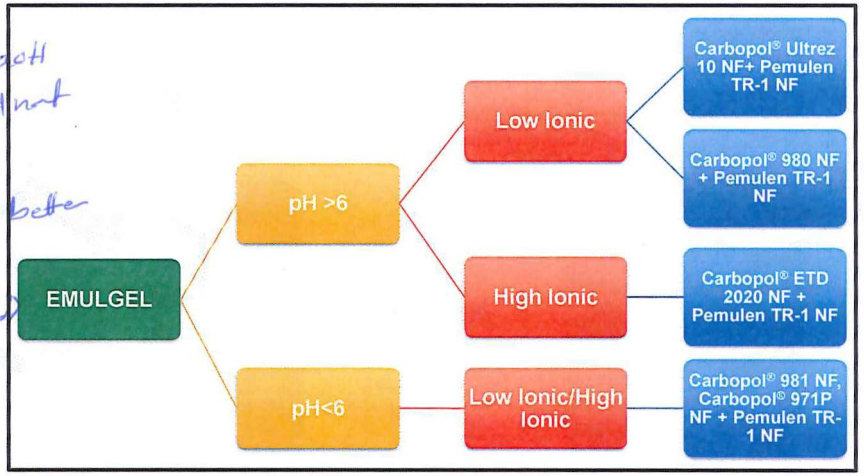
Polymer Selection – Emulgel formulations



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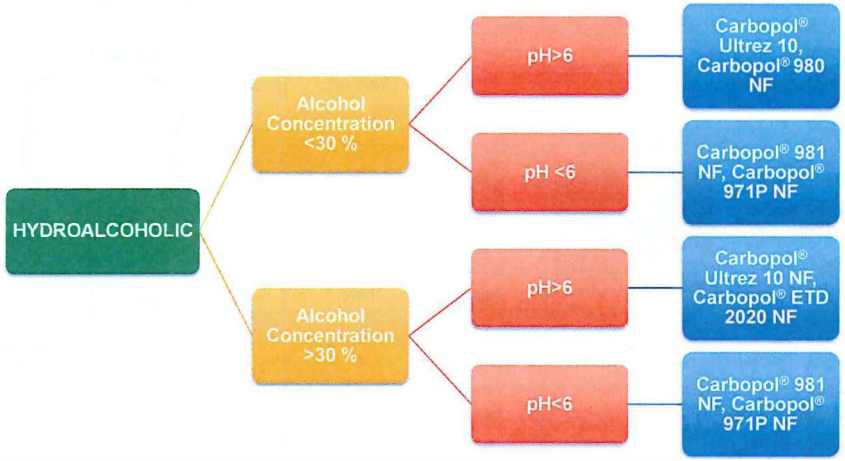
Polymer selection – Hydro-Alcoholic formulations



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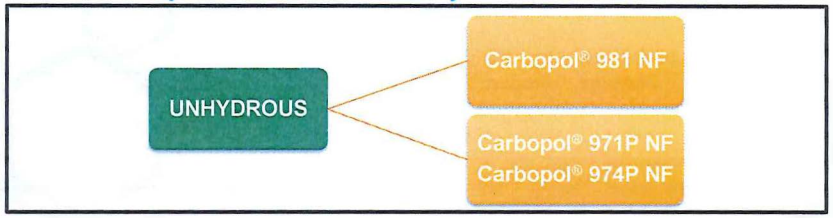
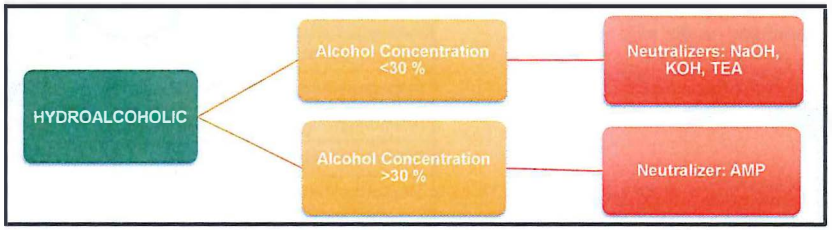
Polymer Selection – Anhydrous formulations



Choice of Neutralizer



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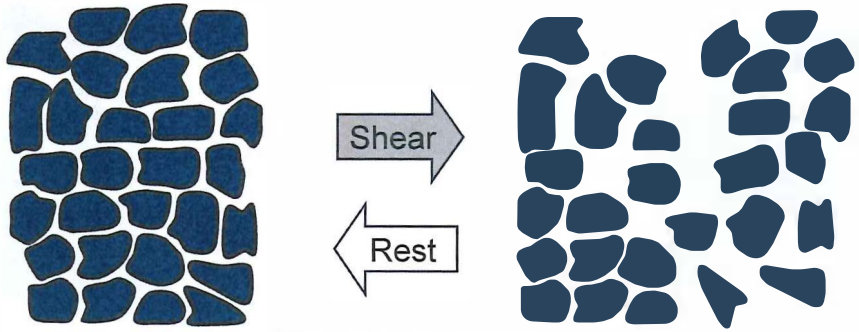
Viscoelastic Dispersions – Shear Thinning

- High viscosity at rest
- Under shear – viscosity decreases (shear thinning)
- After shear stops –high original viscosity quickly recovered
- Rheology useful for pouring, pumping, spreading and spraying → elastic → plastic → Brittle.



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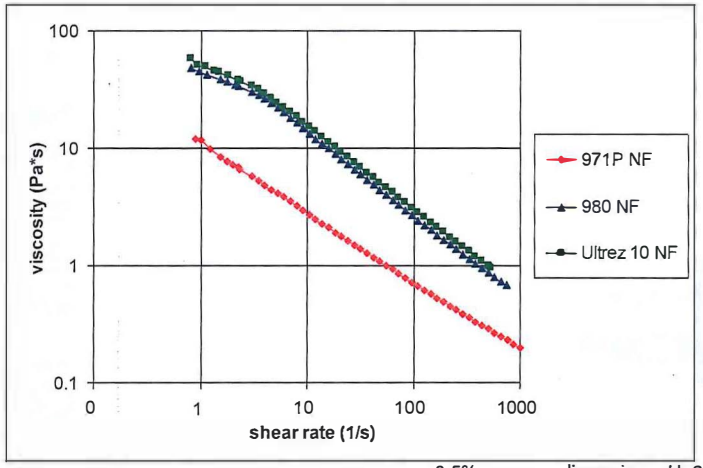
Viscoelastic Dispersions – Shear Thinning



0.5% aqueous dispersion, pH=6

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Suspension stabilization

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Rheology

- Rheology is the study of the deformation and flow of a material when it is subjected to an applied force.
- When force is applied to a material. The measure of a flowing liquid to resist an applied shearing force is called its internal friction or viscosity.
- Flow behaviors are broadly categorized as either Newtonian or non-Newtonian.
- In Newtonian flow, the shear stress and shear rate are always in direct proportion to each other. The viscosity of a Newtonian fluid will always be the same, regardless of the shear stress or shear rate.
- In more complex systems, however, the response to applied stress is nonlinear. These non-Newtonian systems are characterized by large dissolved or solvated molecules, with a tendency to re-associate and a strong interaction with the solvent.

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Thixotropy

- Thixotropy is defined as a decrease in viscosity under stress, followed by gradual recovery when the stress is removed. The effect is time dependent.
- A thixotropic system is one in which (1) shear thinning occurs as stress is increased; and (2) the flow curve is less non-Newtonian when the stress is rapidly removed. A thixotropic material is characterized by the hysteresis loop that is formed when a dispersed polymer has structure which is broken by the shearing force. Upon standing (no shear stress) the structure reforms with time.
- Most Carbopol® polymer gels exhibit little or no thixotropy. Highly viscous media can be spread, stirred or pumped, but when the stress ceases, recovery to the original viscosity is instantaneous

Deformation and reformation due to the elastic property.

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Yield Value

- Yield value is commonly defined as initial resistance to flow under applied stress. In the case of Bingham and Ellis plastic flow, a minimum shear stress is required to initiate flow. This minimum stress is known as the yield value or yield index.
- A practical application of yield value is the suspension of particles in a liquid. Unless the force of gravity operating on a suspended particle of a given mass exceeds the liquid's yield value, it will not descend.
- In most of the range examined, a Carbopol® polymer was ten-to-fifty times more efficient in delivering yield value than other suspending aids such as Carrageenan, Carboxymethyl cellulose, Xanthan gum, Algin, Magnesium aluminum silicate Veegum T, Acrylic emulsion, Acrysol ASE-60, Tragacanth gum, Locust bean gum, Guar gum. Hydroxyethyl cellulose, Hydroxypropyl methylcellulose, Polyethylene oxide and Fumed silica.

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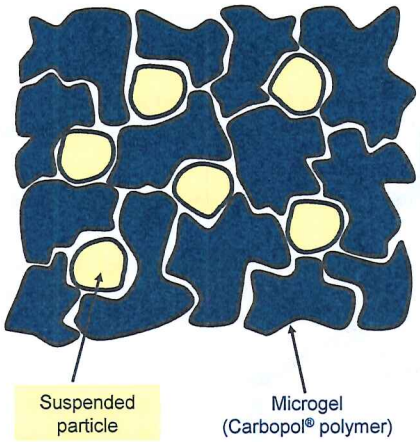
Suspension Stabilization

- Carbopol® polymers swell when hydrated and neutralized, forming a colloidal dispersion.
- The swollen, close-packed microgels are able to hold solid particles within the gel structure – permanent suspension.
- The suspending ability is due to high yield value rather than viscosity.
- Carbopol® polymers provide a wide range of viscosity profiles and have very high yield values, even at low concentrations.



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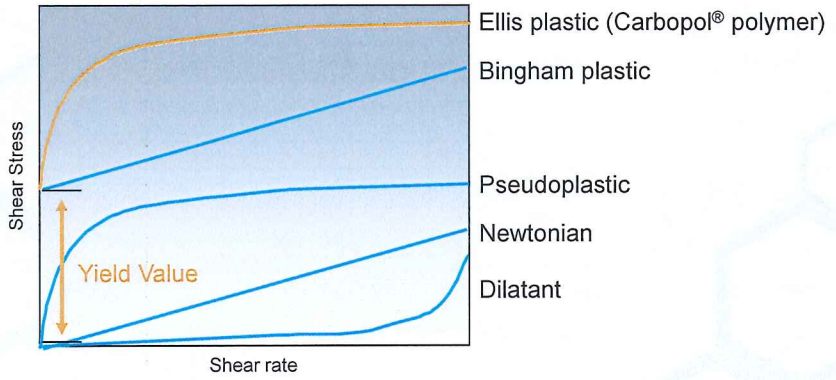
Suspension Stabilization



Yield value - initial resistance to flow under applied stress
Suspending ability of a vehicle – yield value is more important than viscosity

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Suspension Stabilization

- Carbopol® polymers are unique for formulating suspensions that are stable with low levels of polymer
  - Wide range of viscosity profiles
  - Very high yield values, even at low concentrations
- Yield value is more important than viscosity when determining suspending ability of a vehicle.
  - High yield value is necessary to create permanent suspensions
  - Viscosity can only slow down the rate of settling
- Medium/highly crosslinked polymers have higher yield value than lightly crosslinked polymers.
- Applications
  - Suspension stabilization
  - Emulsion stabilization
  - Foam stabilization
  - Vertical cling

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Emulsion Stabilization - Pemulen™ Polymers

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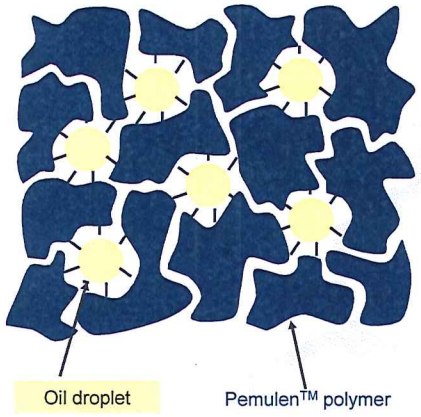
Emulsion Stabilization - Pemulen™ Polymers

Pemulen™ polymers

- Carbomer copolymers of acrylic acid and a long chain alkyl methacrylate crosslinked with allyl ethers of pentaerythritol.
- Have small lipophilic portion in addition to a large hydrophilic portion.
- Form O/W emulsions.

Steric and associative stabilization mechanism:

- Hydrophilic portion forms a gel network around oil droplets.
- Hydrophobic portion anchors in the oil phase.



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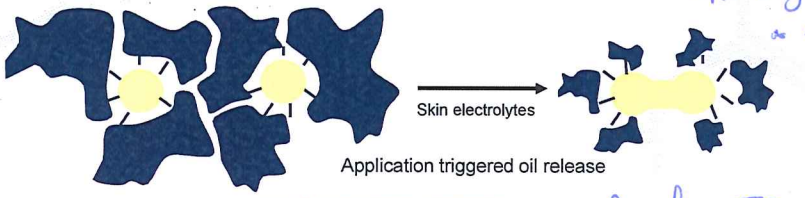
Emulsion Stabilization - Pemulen™ Polymers

Pemulen™ polymers (vs. traditional surfactants) (Macroemulsion).

- Generally independent of oil type(s) / HLB values and level of oils – formulation flexibility
- High efficiency: 0.10 - 0.40 wt%. Use minimum amount of Pemulen™ polymers to achieve emulsion stabilization and, if necessary, adjust viscosity with Carbopol® polymers
- No surfactant required, but it may be combined to achieve smaller droplet size
- Impart viscosity and yield value (suspending properties)
- Shear thinning rheology



• no Lag phase
• no wash off

Pemulen TR = Triggered release

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Emulsion Stabilization - Pemulen™ Polymers

Pemulen™ Polymer	TR-1 NF	TR-2 NF
USP/NF monograph	Carbomer Copolymer Type B	Carbomer Copolymer Type A
Typical oil levels	Up to 20 - 30%	Up to 50%
Typical use level (wt%)	0.20 – 0.40	0.15 – 0.30
pH formulating range	4 - 8	4 - 8
Viscosity (mPa*s) pH 7.3 - 7.8 0.2 wt% emulsion 1.0 wt% dispersion	 6,500 - 15,500 10,000 - 26,500	 1,700 - 4,500 4,500 - 13,500

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Formulation and Processing Considerations

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Formulation Ingredients

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Typical Polymer Usage Levels

Application	Usage Level (wt. %)
Topical aqueous gel	0.5 – 3.0
Topical hydroalcoholic gel	0.5 – 3.0
Topical emulsions	0.1 – 0.4
Oral suspension / solution	0.1 – 1.0

Selection of the suitable polymer

- Review of polymer specifications
- Considerations for regulatory requirements for the final product
- Evaluation of key performance properties in the final product

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Co-Ingredients

- Vehicle
- Neutralizer
- Compatibility
  - electrolytes
  - cationics
  - metals, etc
- Stability considerations
  - preservatives
  - chelating agents, etc

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Carbopol® Polymer Dispersions – Vehicles

- Aqueous vehicles – very common
- Solvent mixture (hydrous and anhydrous) – thickening by hydrogen bonding and /or neutralization
- Choice of vehicle may determine selection of the neutralizer.
- The amine salt of the polymer must be swellable in the solvent system. If not, the product will exhibit low clarity, reduced/no viscosity and/or precipitation.

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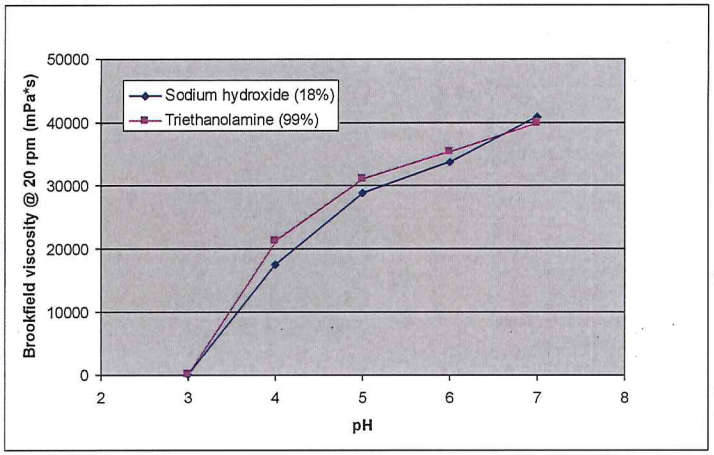
Effect of Neutralizer Type on the Viscosity of 0.5% Carbopol® 980 NF Polymer Dispersion



Similar thickening efficiency of Carbopol® 980 NF polymer in aqueous dispersions neutralized with sodium hydroxide or triethanolamine.

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Formulation Impact of Select Co-Ingredients

Co-Ingredient	Formulation Impact	Recommendations
Electrolytes	• Reduced viscosity • Lower clarity • Multivalent ions cause more serious impact - precipitation	• Minimize electrolytes whenever possible • Increase concentration of the polymer • Add electrolytes after pH adjustment • Select a different Carbopol® polymer grade
Cationics	• Reduced viscosity • Lower clarity • Complexation may cause precipitation	• Use very low levels of cationics • Neutralize before adding cationics • Use cationics with lower charge density and high molecular weight

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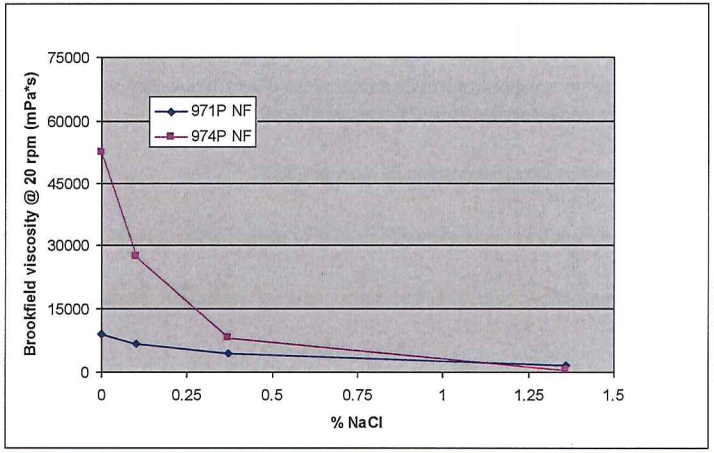
Effect of Salt on the Viscosity of 1.0% Carbopol® 971P NF and 974P NF Polymer Dispersions at pH 6.0



In general, in electrolyte systems lightly crosslinked Carbopol® polymers perform better than highly crosslinked Carbopol® polymers.

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Processing Considerations

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General Processing Recommendations

- Uniformly disperse the polymer in the vehicle, to avoid agglomeration;
  - Fish eyes, non-uniform appearance, viscosity variation, instability
- Allow complete polymer hydration (enough time and mixing), before adding other formulation components
  - Grainy, non-uniform appearance, viscosity variation, instability
- Avoid excessive/improper mixing during dispersion
  - Air entrapment, viscosity variation, instability
- Avoid high shear mixing (limit intensity, number of cycles and duration), especially after pH-adjustment
  - Viscosity loss and instability
- Gradual addition of neutralizer, to allow for pH equilibration
  - Viscosity variation, instability
- Order of addition is critical for avoiding some incompatibilities (ex. electrolytes added after pH-adjustment)
  - Non-uniform appearance, viscosity variation and instability
- Select packaging type and conditions
  - Instability

high shear mixing is done before neutralization because it may lead to loss in viscosity

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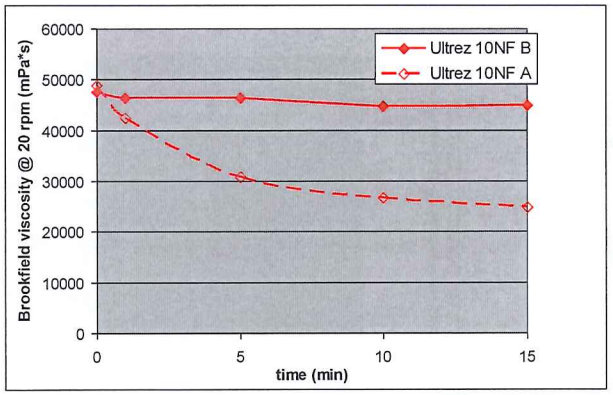
General Processing Recommendations

Effect of mechanical shear

- Vigorous and prolonged mixing causes irreversible viscosity and yield value loss, inconsistent results and stability issues
- Mixers with conventional open-blade impeller (three blade marine impeller) is recommended
- Pumping of the dispersion best done with diaphragm and positive displacement pumps;
- Polymer in a fully swollen stage is more vulnerable to shear force than the un-swollen polymer.



Effect of mechanical shear (Tekmar rotor-stator homogenizer @ 8,500 rpm) applied to polymer dispersion before (B) or after (A) pH adjustment (pH~7)

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Dispersion Preparation – Method Selection

Direct method

- Addition of polymer particles (non-agglomerated) **direct** into the aqueous phase
- Prevent polymer agglomeration – use screen, eductor or mechanical disperser
- Add polymer at the beginning and neutralize at the end of the process
- Versatile – applicable to gels or emulsions, but the polymer may not be easy to disperse (except ETD 2020NF or Ultrez 10NF)

Indirect method

- Pre-dispersion of the polymer in the **non-polar phase** (oil), followed by mixing with the aqueous phase and neutralization
- Applicable to emulsions only
- The polymer may be easily dispersed, but may not work for some oils and loading levels

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Dispersion Preparation – Direct Method

- The polymer is preferably added first to the formulation
- Use water at room temperature for traditional polymers (to avoid longer dispersion time due to polymer agglomeration in the presence of aqueous vapors)
- Disperse polymer in water containing no salts or alkali
- If necessary, add small amount of inorganic acid to reduce viscosity and air entrapment
- After dispersing, allow time for complete polymer hydration (under mixing at lower agitation rate)

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Dispersion Preparation – Direct Method

- Dispersions of Carbopol® polymers – method choice depends on the:
  - Batch size
  - Polymer concentration
  - Available equipment
- Small batches with up to 2% w/w traditional polymer
  - Sift the polymer into the vortex of the moderately agitating liquid, by using a coarse sieve or a stainless steel 20 mesh screen, and mixers with conventional open-blade impeller
- Large batches and/or higher polymer concentrations
  - Disperse the polymer using an eductor
- Large scale with/without continuous dispersion
  - Use mechanical dispersers

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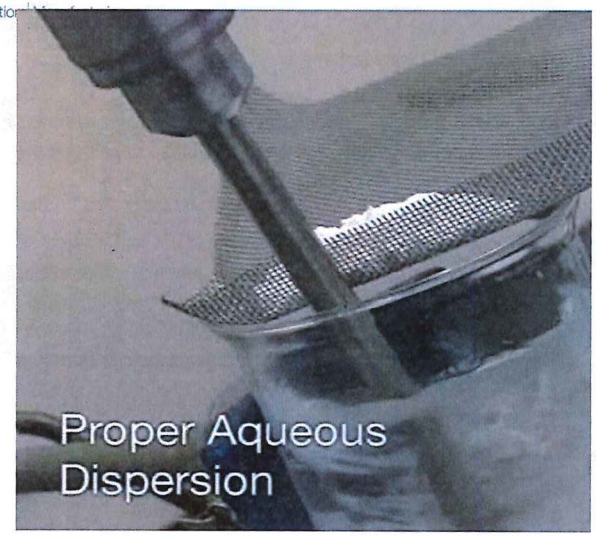
Dispersion Preparation – Direct Method



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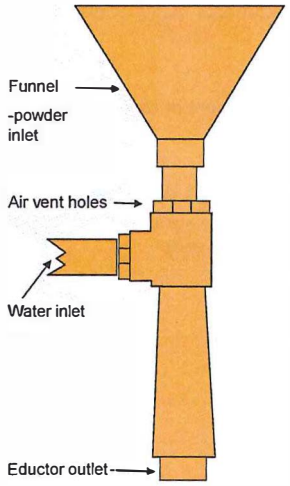
Dispersion Preparation – Direct Method



Eductors –

- Partial vacuum created by bernoulli effect determines polymer uptake;
- Turbulence of the water within the valve rapidly wets out the polymer;
- Constant pressure is required;
- The slurry is transferred into mixing tank to achieve complete hydration

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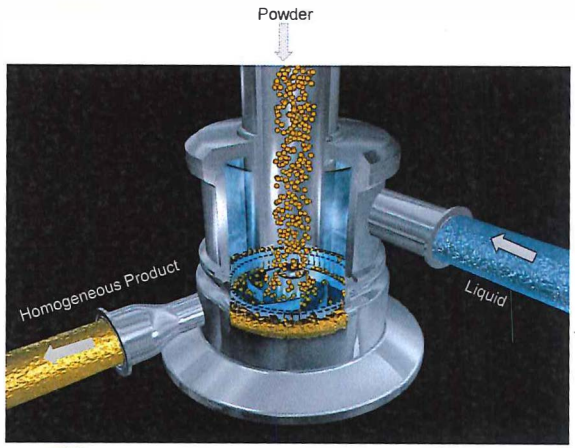
Dispersion Preparation – Direct Method

Mechanical dispersers - use a high velocity eductor coupled with an in-line homogenizer

Quadro Ytron® Powder ZC Disperser

- The powder is drawn in by the strong negative pressure created by the ZC-reactor head.
- Immediately after contacting the liquid phase, the powder is instantly wetted and thoroughly dispersed, before the polymer is fully hydrated.
- Shear forces are applied for an extremely short time - very gentle process.
- In most cases a single pass operation is necessary - highest viscosities achieved for extremely shear-sensitive materials.



Courtesy of Ytron Process Technology Gmbh & Company and Quadro Engineering Corporation

ZC-Reactor Head

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Dispersion Preparation – Direct Method

Dispersions of Carbopol® ETD and Ultrez polymers:

- Polymers can be directly added to water – they wet quickly, yet hydrate slowly:
  - Sprinkle polymer on the surface of water and allow to self-wet (vigorous agitation produces foam);
  - Gently begin agitation.
- Keep agitation to a minimum (to avoid air entrapment) while adding the remaining ingredients to the formulation.
- Lower viscosity of the unneutralized dispersion enables easier handling in mixing tanks and process lines.
- Temperature (<60 °C) may decrease dispersion time.

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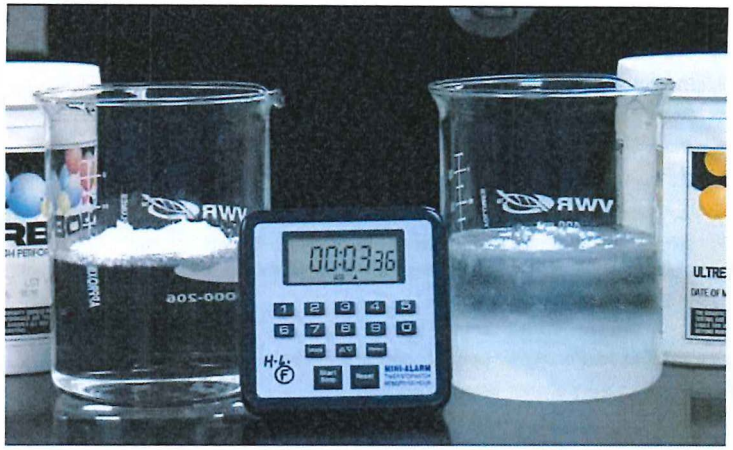
Dispersion with Traditional Carbopol® Polymer vs. Carbopol® Ultrez 10 NF Polymer



Traditional Carbopol® Polymer

Carbopol® Ultrez 10 NF Polymer

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Dispersion Preparation – Indirect Method

- Applicable to emulsions (O/W) only:
  - Polymer is pre-dispersed into the homogeneous oil phase, at room temperature or below 65 °C;
  - Oil dispersion is mixed with the aqueous phase (continue mixing for 20 – 30 minutes); polymer migrates from oil to water phase.
  - pH of the emulsion is adjusted.
- The polymer may be easily dispersed, but may not work for some oils and loading levels.

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Dispersion Preparation

- Incorporating active pharmaceutical ingredients into Carbopol® polymer dispersions - depending on the physical/chemical properties:
  - **Insoluble ingredients** – add before or after pH adjustment of the polymeric dispersion
  - **Soluble ingredients** - dissolve in the water used to prepare the polymeric dispersion. Some soluble ingredients are added to the final formulation to avoid compatibility issues (example, electrolytes added at the end).

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Sterilization

- The formulations containing polymer dispersion may undergo:
  - Steam sterilization (autoclaving) – prevent viscosity loss by reducing the effect of oxidative species (minimize headspace and oxygen permeation into package, add EDTA, etc.);
  - Ionizing radiation (gamma radiation)
  - Aseptic processing - the components of the final dosage form are sterilized separately and the finished article is assembled in an aseptic manner
- Not recommended for carbomer dispersion:
  - dry-heat sterilization
  - gas sterilization
  - sterilization by filtration.

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Equipment Cleaning

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Equipment Cleaning

- Equipment should be promptly cleaned after processing carbomer dispersions.
- Gelled residue may be removed by **power wash** with purified, preferably warm water.
- If an excessive gel layer formed, it may be collapsed using a dilute solution (5% w/v) of salt. NaCl
- Dry residue on the equipment may be soaked using hot dilute alkaline solutions (2-5% w/v), then removed with pressure washing.
- Examples:
  P3-cosa® CIP 95 (Ecolab GmbH & Co. OHG)
  Extran® AP12 (EMD - Merck KGaA)

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Stability and Handling

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Stability and Handling – Carbopol® Polymers as Dry Powder

- **Dust**
  - Fine, light, fluffy powders
  - Normal precautions to prevent loss or hazard from dusting/explosion
- **Moisture**
  - Hygroscopic material
  - As shipped, maximum 2% moisture
  - Typical equilibrium moisture content at 25 C and 50% RH: 8 - 10%
  - Moisture pickup does not affect efficiency of the polymers, but makes them more difficult to disperse and weigh accurately
- **Temperature**
  - Stable under normal processing temperatures and up to ~104 °C (Tg)
  - Exposed to excessive temperatures, may become sintered – more difficult to disperse
  - Complete decomposition in 30 minutes at 260 °C
- **Microbial growth**
  - Does not support microbial growth
- **Stability**
  - Polymers in dry powder state are chemically very stable under normal storage conditions.
  - Polymers stored in sealed, standard Lubrizol containers meet the specification ranges for two years after the production date.
  - Containers must be tightly closed and stored protected from moisture.

shelf life 5 years.

Lubrizol

Ophthalmic Formulations Containing Carbomers or Polycarbophil

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Stability and Handling – Dispersions of Carbopol® Polymers

- Temperature
  - Minimal viscosity change with temperature
  - Freeze-thaw stable
- Oxidative degradation
  - Reactive oxygen species may cause permanent viscosity loss
  - Process catalyzed transition metals and UV
  - Include chelating agents and UV absorbers in the formulation
- Microbial growth
  - Dispersions should include preservatives

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

List of ophthalmic formulations containing Carbomer and/or Polycarbophil

Sr. No.	Name of the product	Active Ingredient/ Indication	Ingredients
1	**Betaxon Ophthalmic Suspension (Alcon Labs USA)**	Levobetaxol HCl 0.5% (Glaucoma/Reduce Intraoccular pressure)	Each mL of BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% contains: **Active:** levobetaxolol HCl 5.6 mg equivalent to 5.0 mg of levobetaxolol free base. **Preservative:** benzalkonium chloride 0.01%. **Inactive:** mannitol, poly(styrene-divinyl benzene) sulfonic acid, Carbomer 974P, boric acid, N-lauroylsarcosine, edetate disodium, hydrochloric acid or tromethamine (to adjust pH) and purified water. It has a pH of 5.5 to 7.5 and an osmolality of 260 to 340 mOsm per kg
2	**Betoptic S Ophthalmic Suspension (Alcon)**	Betaxolol HCl 0.25% (Glaucoma/Reduce Intraoccular pressure)	Each mL of BETOPTIC S® (betaxolol hydrochloride ophthalmic suspension) 0.25% contains: **Active:** betaxolol HCl 2.8 mg equivalent to 2.5 mg of betaxolol base. **Preservative:** benzalkonium chloride 0.01%. **Inactive(s):** Mannitol, Poly(Styrene-Divinyl Benzene) sulfonic acid, Carbomer 934P, edetate disodium, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water. BETOPTIC S® (betaxolol hydrochloride ophthalmic suspension) 0.25% has a pH of approximately 7.6 and an osmolality of approximately 290 mOsmol/kg

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

List of ophthalmic formulations containing Carbomer and/or Polycarbophil

3	**Pilogel Ophthalmic Gel (Alcon)**	Pilocarpine HCl 4% (Glaucoma/Reduce Intraoccular pressure)	The gel contains Pilocarpine 40 mg/g other ingredients are benzalkonium chloride, **Carbomer 940**, disodium edetate, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water
4	**Vexol 1% Ophthalmic Suspension (Alcon)**	Rimexolone 1% (Corticosteroid for post-operative anti-inflammatory effect)	Each mL Contains: **Active:** rimexolone 10 mg (1%) **Preservative:** benzalkonium chloride 0.01%. **Inactive ingredients: Carbomer 974P**, polysorbate 80, sodium chloride, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water. The pH of the suspension is 6.0 to 8.0 and the tonicity is 260 to 320 mOsmol/kg.
5	**Restasis Ophthalmic Emulsion (Allergan)**	Cyclosporine 0.05% (improve tear secretion in dry eye condition)	Each mL of RESTASIS® ophthalmic emulsion contains: **Active:** cyclosporine 0.05% **Inactives:** glycerin; castor oil; polysorbate 80; **Carbomer copolymer type A**; purified water; and sodium hydroxide to adjust pH. It has an osmolality of 230 to 320 mOsmol/kg and a pH of 6.5-8.0

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

List of ophthalmic formulations containing Carbomer and/or Polycarbophil

6	**Fucithalmic Fusidic Acid Eye drops (Leo Pharma)**	Fusidic Acid 1 % (topical treatment of bacterial conjunctivitis)	Each gram contains fusidic acid, hemihydrate 10mg. **Excipient:** 0.01% w/w benzalkonium chloride, disodium edetate, mannitol, **Carbomer**, sodium hydroxide, water for injection
7	**Genteal Severe hypromellose 2910 (4000 mpa.s) (Novartis)**	HPMC 0.3 % (Artificial tears)	Contains **Carbopol 980**, GenAqua (sodium perborate), phosphonic acid, purified water, sodium hydroxide, and sorbitol.
8	**Viscotears (Novartis)**	Carbomer 980 NF 0.2 % (Artificial tears)	Viscotears contains 2.0 mg/g of the **active ingredient, Carbomer (polyacrylic acid).** The liquid gel also contains the inactive ingredients cetrimide (as a preservative), sorbitol, sodium hydroxide and water.
9	**Liposic (Bausch and Lomb)**	Carbomer 980 NF 0.2 % (Artificial Tears)	Each tube contains 2.0 mg of **Carbomer** in each 1 g of gel. The other ingredients are cetrimide, sorbitol, medium-chain triglycerides, sodium hydroxide (for pH adjustment) and purified water.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

List of ophthalmic formulations containing Carbomer and/or Polycarbophil

10	**Azopt (Alcon)**	Brinzolamide 1 % (Glaucoma/Reduce Intraoccular pressure)	Each mL of AZOPT® (brinzolamide ophthalmic suspension) 1% contains: **Active ingredient:** brinzolamide 10 mg. **Preservative:** Benzalkonium chloride 0.1 mg. **Inactives:** mannitol, **Carbomer 974P**, tyloxapol, edetate disodium, sodium chloride, purified water, with hydrochloric acid and/or sodium hydroxide to adjust pH.
11	**Ilevro Nevenac (Alcon)**	Nefapenac 0.3 % (NSAID reduce pain and inflammation)	Each mL of ILEVRO* (nepafenac ophthalmic suspension), 0.3%, contains: **Active:** nepafenac 0.3% **Inactives:** boric acid, propylene glycol, **Carbomer 974P**, sodium chloride, guar gum, carboxymethylcellulose sodium, edetate disodium, benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust pH and purified water, USP.
12	**Zirgan Gel (Bausch and Lomb)**	Ganciclovir 0.15 % (Antiviral for Eye infections caused by herpes simplex virus)	Each gram of gel contains: **Active:** ganciclovir 1.5 mg (0.15%). **Inactive: Carbomer Homopolymer**, water for injection, sodium hydroxide (to adjust the pH to 7.4), mannitol. **Preservative:** benzalkonium chloride 0.075 mg.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

List of ophthalmic formulations containing Carbomer and/or Polycarbophil

13	**Simbrinza suspension (Alcon)**	Brinzolamide 1 % Brimonidine Tartarate 0.2 % (Glaucoma/Reduce Intraoccular pressure)	Each mL of SIMBRINZA (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% contains: **Active:** brinzolamide 10 mg, brimonidine tartrate 2 mg (equivalent to 1.32 mg as brimonidine free base); **Preservative:** benzalkonium chloride 0.03 mg; **Inactive ingredients:** propylene glycol, **Carbomer 974P**, boric acid, mannitol, sodium chloride, tyloxapol and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.
14	**Systane Gel (Alcon)**	Hypromellose 0.3 % (Artificial Tears)	**Carbopol 980**, phosphonic acid, purified water, sodium perborate and sorbitol. May contain sodium hydroxide to adjust pH.
15	**Refresh Optive drops (Allergen)**	Carboxymethylcellulose sodium 0.5% Glycerin 1% Polysorbate 80 0.5% (Lubricant and moisturizer for dry eye)	Contains **Active:** Carboxymethylcellulose sodium 0.5% Glycerin 1% Polysorbate 80 0.5% **Inactive:** Boric acid; **Carbomer copolymer type A**; castor oil; erythritol; levocarnitine; purified water; and sodium hydroxide.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

List of ophthalmic formulations containing Carbomer and/or Polycarbophil

16	**Basivance suspension (Bausch and Lomb)**	Besifloxacin 0.6 % (Durasite technology) (Fourth generation broad spectrum antibiotic)	Each mL Contains: **Active:** besifloxacin 0.6% (6 mg/mL); **Preservative:** benzalkonium chloride 0.01% **Inactive:** Polycarbophil, mannitol, poloxamer 407, sodium chloride, edetate disodium dihydrate, sodium hydroxide and water for injection. Besivance is an isotonic suspension with an osmolality of approximately 290 mOsm/kg.
17	**Azasite (Akorn)**	Azithromycin 1 % (Antibiotic)	AzaSite (azithromycin ophthalmic solution) is a 1% sterile aqueous topical ophthalmic solution of azithromycin formulated in DuraSite® (Polycarbophil, edetate disodium, sodium chloride). AzaSite is an off-white, viscous liquid with an osmolality of approximately 290 mOsm/kg. **Preservative:** 0.003% benzalkonium chloride. **Inactives:** mannitol, citric acid, sodium citrate, poloxamer 407, Polycarbophil, edetate disodium (EDTA), sodium chloride, water for injection, and sodium hydroxide to adjust pH to 6.3.
18	**Lotemax Gel (Bausch and Lomb)**	Loteprednol Etabonate 0.5 % (Loteprednol is an ophthalmic corticosteroid. It decreases inflammation (eg, redness, swelling, warmth, pain) of the eye.	Each gram contains: **Active:** Loteprednol Etabonate 5 mg (0.5%); **Inactive:** Boric acid, edetate disodium dihydrate, glycerin, Polycarbophil, propylene glycol, sodium chloride, tyloxapol, water for injection, and sodium hydroxide to adjust to a pH of between 6 and 7. **Preservative:** benzalkonium chloride 0.003%.

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Liquid and Semisolid Dosage Forms Containing Carbomers or Polycarbophil

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Liquid and semisolid products for oral or peroral administration

Product/Company	API	Dosage Form	Admin route	Excipients
Biaxin Granules Abbott Laboratories	**Clarithromycin** 125 mg/5 ml/-250 mg/5 ml	Suspension (granules for suspension)	Peroral	Carbomer, castor oil, citric acid, hypromellose phthalate, maltodextrin, potassium sorbate, povidone, silicon dioxide, sucrose, xanthan gum, titanium dioxide and fruit punch flavor.
VIRAMUNE® Oral Suspension Boehringer Ingelheim	**Nevirapine** 50 mg/5 ml	Suspension	Peroral	Carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide and purified water.
Sab simplex® Suspension Parke-Davis/Pfizer Pharma	**Simethicone** 69.19 mg/1 ml	Suspension	Peroral	Carbomer 974, Citronensäure 1H2O, Hypromellose, Natriumcitrat H2O-frei, Natriumbenzoat, Natriumcyclamat, Macrogolstearylether, Saccharin-Natrium, Sorbinsäure, Himbeeraroma 60373 H & R, Vanille-Aroma 200817, gereinigtes Wasser.
Gaviscon Advance Pfefferminz Suspension Reckitt Benckiser	**Sodium alginate** 1 g/10 ml **Potassium bicarbonate** 0.2 g/10 ml	Suspension	Peroral	Calciumcarbonat, Carbomer 974P, Methyl-4-hydroxybenzoat (E 218), Propyl-4-hydroxybenzoat (E 216), Saccharin-Natrium, Pfefferminz-Aroma, Natriumhydroxid, ger. Wasser.
Lederlind® Mundgel RIEMSER	**Nystatin** 22.73 mg/g	Gel	Oral cavity	Hymetellose, Carbomer 934, Natriumhydroxid, Glycerol, Methyl-4-hydroxybenzoat, Propyl-4-hydroxybenzoat, Natriumcalciumedetat, Orangenaroma, gereinigtes Wasser.
Kamistad®-Gel STADA	**Lidocaine hydrochloride** 20 mg/g **Chamomile flowers extract** 185 mg/g	Gel	Oral cavity	Benzalkoniumchlorid, Ethanol 96%, Methansäure, Polyacrylsaure, Saccharin-Natrium, Trometamol, gereinigtes Wasser, Wasser, Zimtöl.
Sensodyne® PROSCHMELZ Fluorid Gelée Dentalgel GlaxoSmithKline Consumer Healthcare	**Sodium fluoride** 2.765 g/100 g	Dental gel	Oral cavity	Ger. Wasser, Dinatriumhydrogenphosphat, Carbomer 956, Natriumdodecylsulfat, Aromastoffe, Saccharin-Natrium, Natriumhydroxid, Patentblau V (E 131).

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Polymers | Formulation | Manufacturing

Liquid and semisolid products for skin administration

Product/Company	API	Dosage Form	Admin route	Excipients
Betnesol®-V crinale 0,1% Lösung GlaxoSmithKline	**Betamethasone valerate** 1.22 mg/g	Solution	Skin	Carbomer 980, 2-Propanol, Natriumhydroxid, gereinigtes Wasser
Metrolotion® Emulsion Galderma	**Metronidazole** 7.5 mg/g	Emulsion	Skin	Carbomer 941, Benzylalkohol, Glycerol, Macrogol 400, Macrogolstearylether-21, Macrogolglycerolstearate, Stearylalkohol, dünnflüssiges Paraffin, Cyclomethicon, Kaliumsorbat, Milchsäure- u./od. Natriumhydroxid-Lsg. (zur pH-Wert-Einstell.), ger. Wasser
Aknefug® Oxid Wash Wolff	**Benzoyl peroxide** 4 g/100 g	Suspension	Skin	Carbomer 980, Natriumedetat, Natriumhydroxid, Dodecylpoly(oxyethylen)-2-hydrogensulfat-Natriumsalz, α-Stearoyl-ω-stearoyloxypoly(oxyethylen)-3, gereinigtes Wasser.
VANOS® (fluocinonide) cream, 0.1% Patheon, Inc.	**Fluocinonide** 1 mg/g	Cream	Skin	propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, carbomer 980 NF, diisopropanolamine, and citric acid USP.
Ebenol® leicht 0,25% Crème Strathmann	**Hydrocortisone acetate** 0.25 g/100 g	Cream	Skin	Carbomer-Copolymer (Type B) , Natriumedetat, Natriumhydroxid, Macrogol 400, Decyloleat, Isopropylmyristat, Isopropylpalmitat, dickflüssiges Paraffin, 2-Propanol, gereinigtes Wasser.
Voltaren® Emulgel® Gel Novartis	**Diclofenac diethylamine** 1.16 g/100 g	Gel	Skin	Carbomer 974P, Octan-/Decansäurefettalkoholester, Cetomacrogol 1000, N-Ethylethanamin, 2-Propanol, dickfl. Paraffin, Parfumcreme, Propylenglycol, gereinigtes Wasser.
Divigel® Gel Upsher-Smith Laboratories, Inc.	**Estradiol** 0.1%	Gel	Skin	Carbomer, ethanol, propylene glycol, purified water, and triethanolamine.
Heparin STADA® 60.000 I.E. Gel STADApharm	**Heparin sodium** 60000 I.E./ 100 g	Gel	Skin	Carbomer 980, Macrogolglycerolhydroxystearat, Propylenglycol, 2-Propanol, Trometamol, gereinigtes Wasser, Citronellöl, Lavendelöl.
EMLA® PFLASTER AstraZeneca	**Lidocaine** 25 mg **Prilocaine** 25 mg	Plaster	Skin	Poly(oxyethylen)-54-hydriertes-rizinusöl, Carbomer 974P, Natriumhydroxid (zur pH-Wert-Einstellung), gereinigtes Wasser, Cellulosepulver, Polyethylen, Poly(acrylamid-co-isooctylacrylat), gebleichte Trennfolie beschichtet mit Polyethylen und silikonisiert.

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Liquid and semisolid products for rectal and vaginal administration

Product/Company	API	Dosage Form	Admin route	Excipients
Claversal® Merckle Recordati	**Mesalamine** 4 g/60 g	Suspension	Rectal	Natriumbenzoat (E 211), Kaliummetabisulfit (E 224) (entspr. max. 0,16 g SO2), **Carbomer 934**, Natriumedetat, Kaliumacetat, Xanthangummi, ger. Wasser
Cordes® Estriol Vaginalcreme APS	**Estriol** 0.5 mg/g	Cream	Vaginal	Phenoxyethanol, Cetylstearylalkohol, Macrogol-20-glycerolmonostearat, Glycerolmonostearat, Isopropylmyristat, **Carbomer**, Natriumhydroxid, gereinigtes Wasser
Vagi-Metro® Creme Vaginalcreme Drossapharm	**Metronidazole** 5 g/ 100 g	Cream	Vaginal	Cetylstearylalkohol, selbstemulgierendes Glycerolmonostearat (Tegin), Isopropylmyristat, Natriumhydroxid, Macrogol-20-glycerolmonostearat, Propylenglycol, **Carbomer 34000 mPaS**, Gereinigtes Wasser, konserviert mit Chlorphenesin
Crinone® 8% Vaginalgel Serono	**Progesterone** 90 mg/1.125 g	Gel	Vaginal	Sorbinsäure 0,9 mg, Glycerol, dünnflüssiges Paraffin, hydriertes Palmölglycerid, **Carbomer 974P**, **Polycarbophil**, Natriumhydroxid, gereinigtes Wasser
Rephresh® sanol Vaginalgel	carbomer 934P, glycerol, polycarbophil	Gel	VAGINAL	sodium hydroxide, water for injections, ethyl 4-hydroxybenzoate, methyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate
Replens® sanol Vaginalgel	carbomer 934P, glycerol, hydrogenated palm oil glycerides, thin paraffin, polycarbophil	Gel	VAGINAL	sodium hydroxide, sorbic acid, purified water

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Lubrizol References

Pharmaceutical Bulletins and Technical Data Sheets:

- Bulletin 1 Polymers For Pharmaceutical Applications
- Bulletin 3 Polymer Handling and Storage
- Bulletin 4 Dispersion Techniques For Lubrizol Pharmaceutical Polymers
- Bulletin 5 Neutralization Procedures
- Bulletin 6 Thickening Properties
- Bulletin 7 Flow and Suspension Properties
- Bulletin 8 Emulsification Properties
- Bulletin 21 Formulating Semisolid Products
- Bulletin 22 Oral Suspensions

http://www.lubrizol.com/Pharmaceutical/Literature.html

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Conclusions

Lubrizol pharmaceutical polymers provide key benefits in liquid and semisolid dosage forms

- **Versatile and efficient**
  - Provide rheology modification for aqueous, anhydrous and hydroalcoholic systems at low usage levels
  - Compatible with most acidic, basic and neutral drugs
  - Applications across a broad pH range (4.5 – 10.0)
  - No heat sensitivity compared to other thickening agents
- **Multi-functional**
  - Highly efficient thickening, emulsion and suspension stabilization
  - Can increase bioavailability of active pharmaceutical ingredients due to their bioadhesive properties
- **Safety and quality**
  - Demonstrated to have low irritancy and non-sensitizing properties
  - Manufactured under cGMP conditions
  - Consistent and reproducible properties due to their synthetic nature
  - Do not support microbial growth

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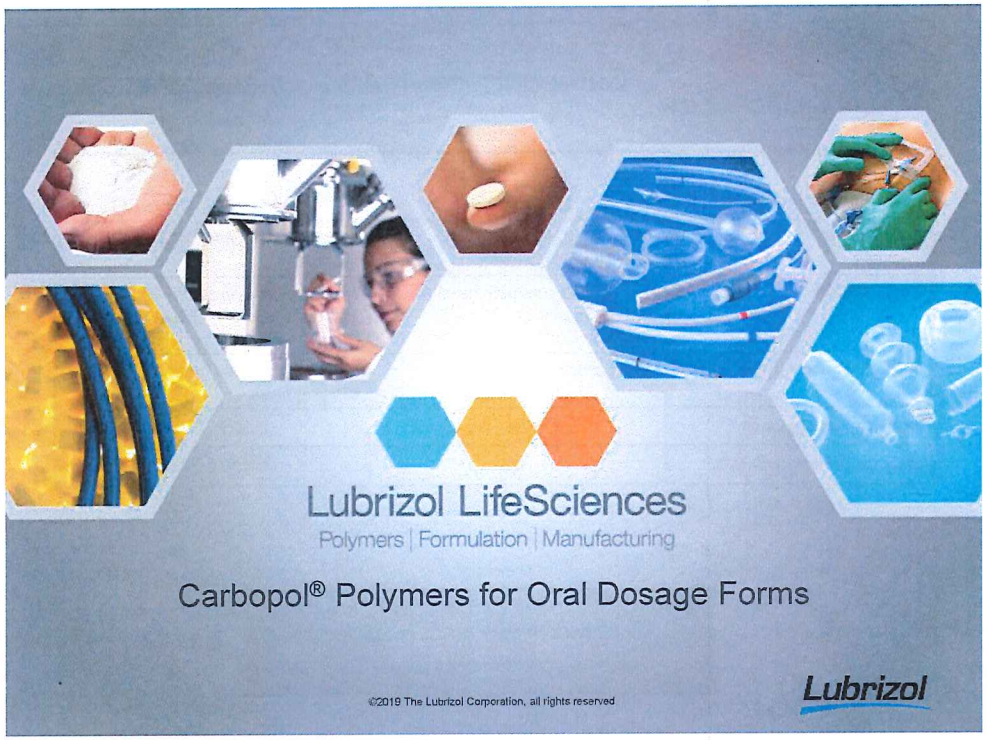

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Attributes of Carbopol® Polymers Important for Controlled Release

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Oral Dosage Forms using Carbopol® Polymers

- Attributes of Carbopol polymers important for oral dosage forms
- Carbopol polymers for hydrophilic matrix tablets – formulation and processing
- Designing multiparticulates with Carbopol polymers
- Multimedia dissolution profile studies
- Carbopol Polymers for Oral Suspensions/Solutions

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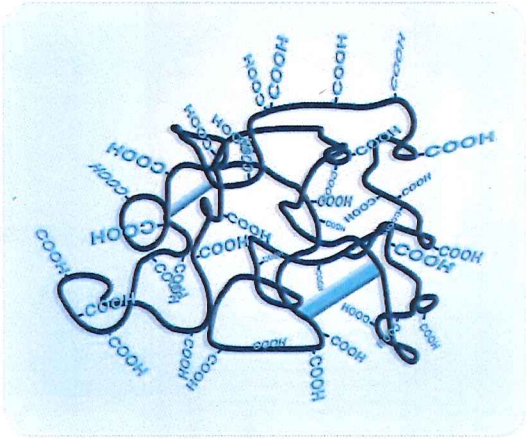
Carbopol® Polymers and Noveon® Polycarbophil

- High molecular weight polymers of acrylic acid
- Chemically cross-linked



Monomer
$CH_2CH(COOH)$
MW = 72

- pKa = 6.0 ± 0.5

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Lubrizol Pharmaceutical Polymers

Carbopol® Polymers

Homopolymers

71G NF
971P NF
974P NF
934P NF 934 NF
940 NF 941 NF
980 NF
981 NF
5984 EP

Copolymer

1342 NF

Interpolymers

ETD 2020 NF
Ultrez 10 NF

Pemulen™ Polymers

Copolymers

TR-1 NF
TR-2 NF

Noveon® Polycarbophil

Polycarbophil

AA-1 USP

Polymerization Solvents

- Ethyl Acetate
- Cosolvent Mixture of Ethyl Acetate and Cyclohexane
- Benzene

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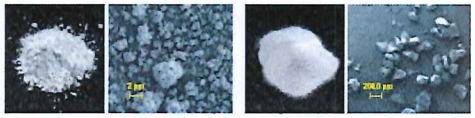
Polymers Formulation Manufacturing

Carbopol® Polymers – Characteristics

Characteristics	Carbopol® Polymer (powders)	Carbopol® 71G NF Polymer (granular)
Description	White, light, fluffy, acidic, hygroscopic powders	White, free flowing, hygroscopic granules
Particle size	Flocculated powders have a median diameter of 2 to 7 microns (Coulter Counter).	Typical size range (min 85%) is 150 - 425 microns (sieve analysis)
Particle morphology (SEM)	Fine particles	Mostly large solid chunks with clinging fines
Bulk density (g/cm³)	~0.2	0.325 - 0.400
Tapped density (g/cm³)	~0.3	0.400 - 0.465



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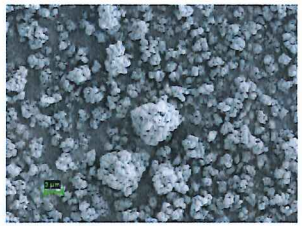
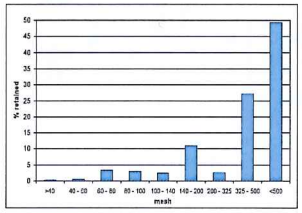
Carbopol® Polymers – Characteristics

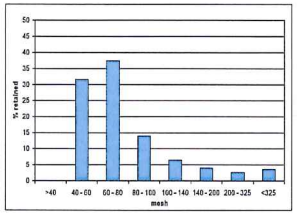


SEM of Carbopol® 971P NF polymer

SEM of Carbopol® 71G NF polymer



Typical particle size distribution of Carbopol® 971P NF polymer



Typical particle size distribution of Carbopol® 71G NF polymer

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Carbopol® Polymers – Characteristics

Characteristics	Carbopol® Polymers
Solubility/swelling properties	The polymers are not soluble due to their crosslinked nature and high molecular weight. The polymers swell in water and some polar solvents (neutralization may be required in some systems), producing viscous dispersions.
Equivalent weight	76 ± 4
Dissociation constant	pKa = 6.0 ± 0.5
Chemical stability	Chemically very stable under normal storage conditions; no significant changes of the chemical parameters or detected impurities for a period of minimum 5 years.
Physical stability	The polymers are hygroscopic
Equilibrium moisture content (25 °C and 50% RH)	8 - 10% w/w
Glass transition temperature	~105°C. Glass transition temperature significantly decreases in the presence of moisture.
Thermal stability	Thermally stable under normal conditions. When exposed to excessive temperatures, above the glass transition temperature, the polymers become sintered. The products may become discolored depending on the temperature and exposure time. Complete decomposition occurs within 30 minutes when heated at 260°C.
Recommended storage	In airtight containers, protected from moisture and excessive temperature.

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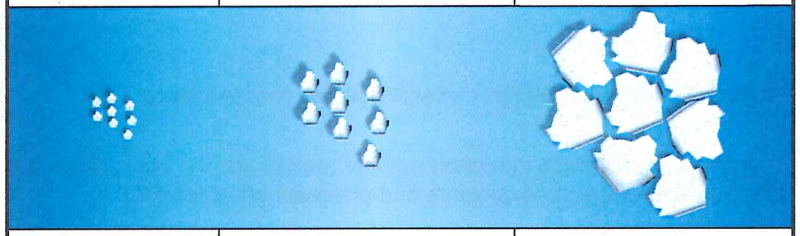
Polymers Formulation Manufacturing

Carbopol® Polymers - Swelling

Dry Polymer	Hydrated Polymer	Neutralized Polymer
		
Ø = 2 - 7µm	pH = 3.0	Ø = 20- 70µm pH = 7.0

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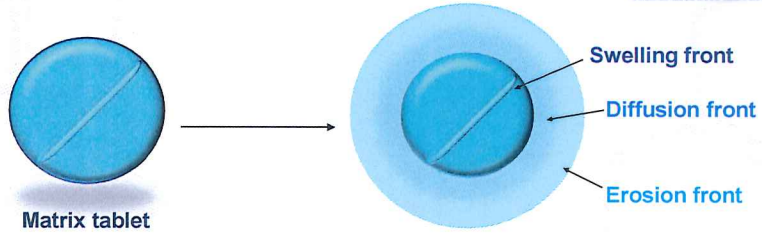
Polymers Formulation Manufacturing

Drug Release From Tablets with Carbopol® Polymers

- Carbopol polymers are efficient **matrix**-forming excipients.
- Drug release is controlled by drug diffusion through the gel layer:
  - Water penetration
  - Polymer hydration and swelling
  - Drug dissolution and diffusion
  - Matrix erosion



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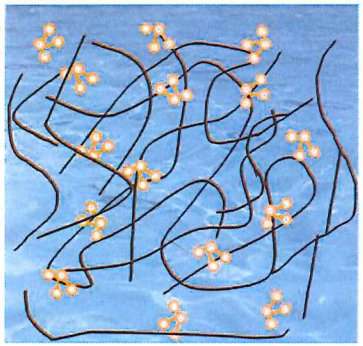
Polymers Formulation Manufacturing

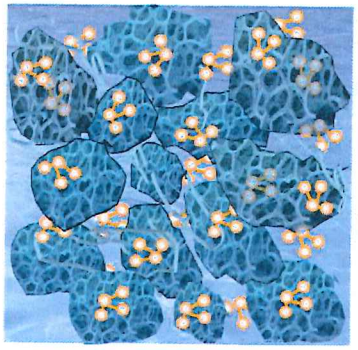
Carbopol polymer will not dissolve during drug release.

Drug Release from Hydrophilic Matrix Tablets

Linear polymer



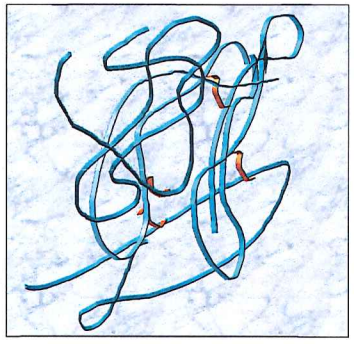
Crosslinked polymer



Lubrizol LifeSciences
Polymers Formulation Manufacturing

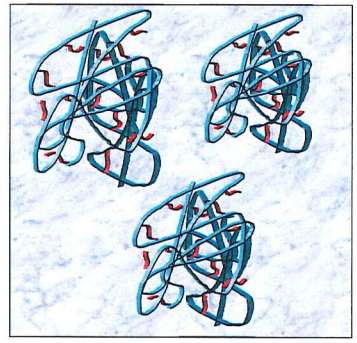
Drug Release from Tablets with Carbopol® Polymers

Carbopol® 971P NF polymer
lightly crosslinked



"Fishnet" structure

Carbopol® 974P NF polymer
highly crosslinked



"Fuzzball" structure

Hydration and swelling of the polymer (crosslink density, chain entanglement) affect the drug release rates.

Lubrizol

Carbopol® Polymers for Hydrophilic Matrix Tablets - Formulation

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Effect of Polymer Type and Level on Drug Release

- Carbopol polymers are highly effective at low concentrations
- Typical usage levels in extended release tablets are 5 – 30%, depending on the drug properties, co-excipients and processing parameters
- At low usage levels, Carbopol polymers are more effective than linear (cellulosic) materials in sustaining the drug release

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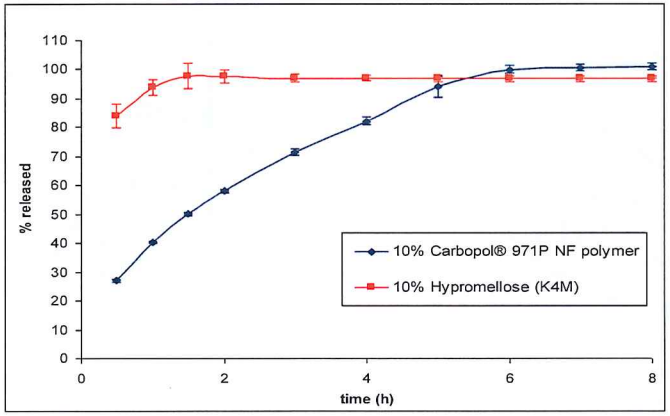
Polymers Formulation Manufacturing

Effect of Polymer Type on Drug Release

Guaifenesin release from wet granulated tablets with 10% polymer was slower for carbomer (Carbopol® 971P NF polymer) than hypromellose (Methocel™ K4M)



Guaifenesin release (USP apparatus 2, 0.1N HCl) from wet granulated tablets

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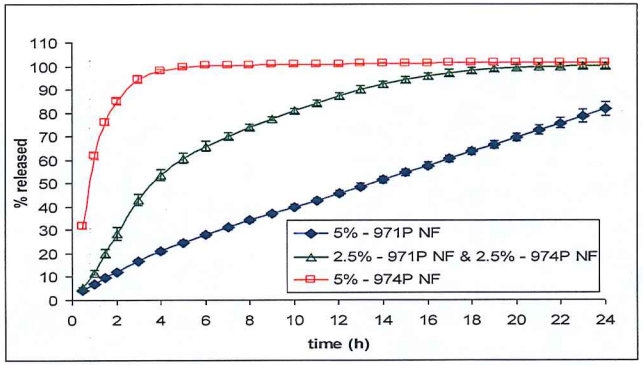
Polymers Formulation Manufacturing

Effect of Carbopol® Polymer Type on Drug Release

Lightly crosslinked Carbopol polymers tend to be more efficient in controlling the drug release than highly crosslinked Carbopol polymers. Intermediate drug release can be achieved by combining Carbopol 971P NF and 974P NF polymers.



Ketoprofen 200 mg release (USP apparatus 2, pH=6.8 buffer) from wet granulated tablets

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Polymers Formulation Manufacturing

Effect of Carbopol® Polymer Level on Drug Release

- Generally, increasing the level of Carbopol polymer in a formulation leads to slower and more linear drug release - the gel layer formed around the tablet becomes stronger, with less regions of low micro viscosity in the swollen tablet (fewer interstitial spaces between the microgels).
- Varying the polymer inclusion level is an effective way to modulate drug release.

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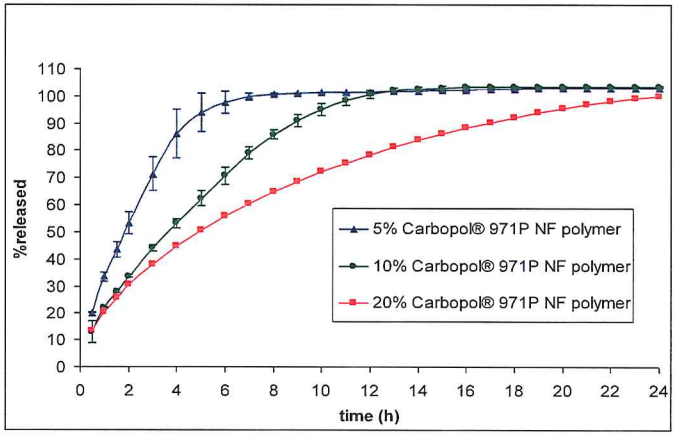
Polymers Formulation Manufacturing

Effect of Carbopol® Polymer Level on Drug Release

Slower and less variable Guaifenesin release from tablets prepared by wet granulation was observed with increasing amounts of Carbopol 971P NF polymer (5% to 20%)



Guaifenesin release (apparatus 2, 0.1N HCl) from wet granulated tablets with Carbopol 971P NF polymer - Guaifenesin 600 mg tablets

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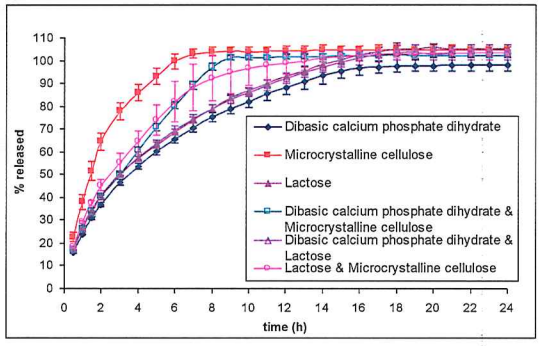
Polymers Formulation Manufacturing

Recommended Co-Excipients



Theophylline release (apparatus 2, USP method for modified release)

Theophylline release from direct compressible tablets with 30% Carbopol 71G NF polymer: microcrystalline cellulose > lactose > dibasic calcium phosphate

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Polymers Formulation Manufacturing

Recommended Co-Excipients *(continued)*

Potential benefits of combinations of Carbopol® polymers with other controlled release excipients:

- Lower total controlled release agent due to synergistic interaction
- Flexibility in delivering target release profiles by varying the ratio and the total amount of the controlled release excipients
- Lower variability in the drug release profiles
- Better flow properties of the formulation blends by using Carbopol 71G NF polymer in combination with polymers with low flowability
- Bioadhesive properties

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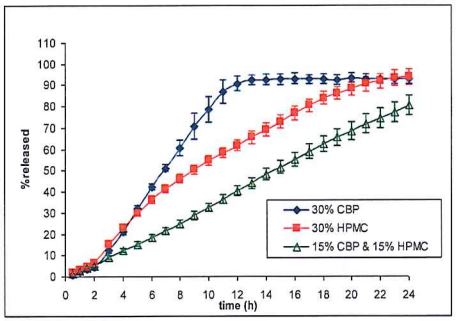
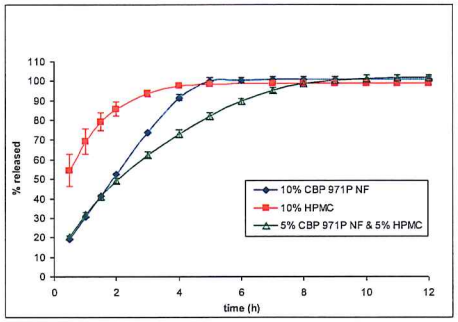
Polymers Formulation Manufacturing

Recommended Co-Excipients *(continued)*



Ketoprofen release (USP method for modified release) from tablets (50 mg) with 30% polymer (direct compression)



Guaifenesin release in pH=6.8 buffer from tablets (100 mg) with 10% polymer (wet granulation)

The release is faster in the presence of Acidic media

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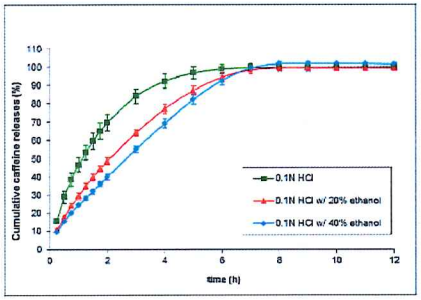
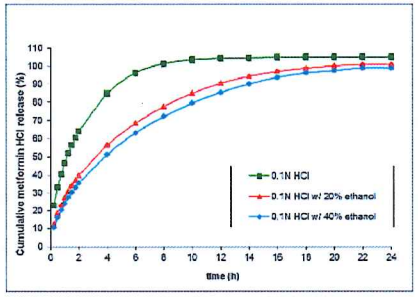
Polymers Formulation Manufacturing

Effect of Alcohol on Drug Dissolution from Tablets Formulated with Carbopol® Polymers



Influence of ethanol on the dissolution of caffeine (200 mg) tablets with 10% w/w Carbopol 971P NF polymer in 0.1N HCl



Influence of ethanol on the dissolution of metformin hydrochloride (750 mg) tablets with 9% w/w Carbopol 971P NF polymer and 7% w/w Carbopol 71G NF polymer in 0.1N HCl

Slower drug release was observed for caffeine and metformin hydrochloride tablets exposed to 20 or 40% v/v ethanol solution compared with exposure to 0.1N HCl

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Polymers Formulation Manufacturing

Effect of Alcohol on Drug Dissolution from Tablets Formulated with Carbopol® Polymers

- Investigate the risk of alcohol-induced dose dumping from extended release tablets formulated with Carbopol polymers
- Based on methodology suggested by the Office of Generic Drugs (U.S. FDA) for evaluating alcohol-induced dose dumping

USP apparatus I (100 rpm) or II (50 rpm)
900 ml of 0.1N HCl Solution containing ethanol (0, 20, and 40% v/v)

- Tablet Formulations Evaluated
  - Manufactured by wet granulation
  - Guaifenesin (600 mg) with Carbopol 971P NF (10% and 20%)
  - Caffeine (200 mg) with Carbopol 971P NF (10%)
  - Metformin Hydrochloride (750 mg) with Carbopol® 971P NF (9%) and Carbopol 71G NF (7%) polymers

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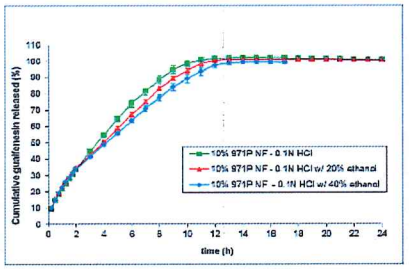
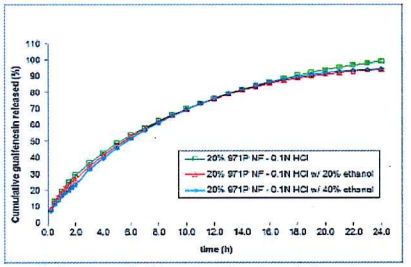
Polymers Formulation Manufacturing

Effect of Alcohol on Drug Dissolution from Tablets Formulated with Carbopol® Polymers



Influence of ethanol on the dissolution of guaifenesin (600 mg) tablets with 10% w/w Carbopol 971P NF polymer in 0.1N HCl



Influence of ethanol on the dissolution of guaifenesin (600 mg) tablets with 20% w/w Carbopol 971P NF polymer in 0.1N HCl

- No alcohol effect was observed for tablets formulated with 20% Carbopol polymer
- For guaifenesin, slightly slower drug release in the presence of alcohol was observed for tablets containing 10% w/w Carbopol polymer
- Alcohol-induced dose dumping was not observed for the formulations tested, thus indicating the robustness of these extended release systems formulated with Carbopol polymers.

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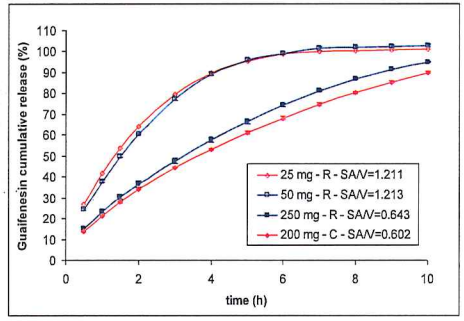
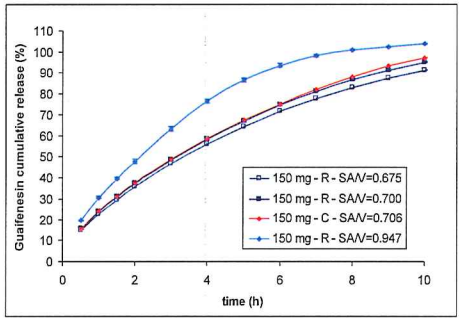
Polymers Formulation Manufacturing

Carbopol® Polymers for Multiple Strength Tablets

- Drug release from multiple strength tablets having the same percent composition is affected by the ratio of surface area / volume ratio (SA/V).
- Typically, tablets with larger SA/V have faster release profiles, regardless of the dose or shape.



Guaifenesin release in pH=6.8 buffer from tablets (25 – 250 mg / tablet) having extreme dose or SA/V



Guaifenesin release in pH=6.8 buffer from tablets (150 mg / tablet) having different shape (R=round; C=capsule) or SA/V

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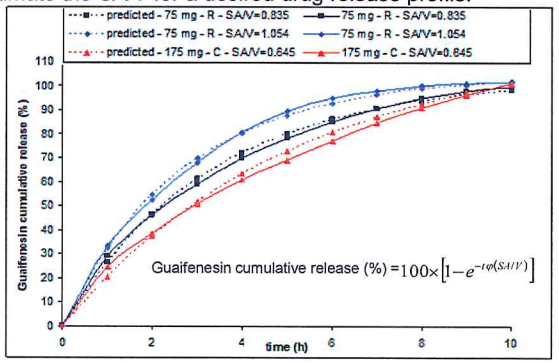
Polymers Formulation Manufacturing

Carbopol® Polymers for Multiple Strength Tablets

A mathematical model may be developed to describe the dynamics of the drug release as function of SA/V and time. The model can work as a tool for tablet analysis and design to:

- Predict the drug release process, based on SA/V
- Estimate the SA/V for a desired drug release profile.



Predicted and actual release from guaifenesin tablets

Pred. shape have critical role in drug release

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Carbopol® 71G NF Polymer Applications

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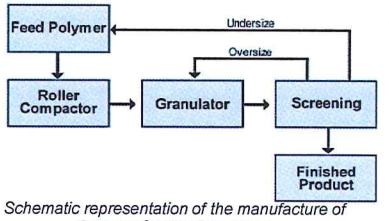
Carbopol® 71G NF Polymer

- Granular form of Carbopol 971P NF polymer (chemically the same polymer, with no other additives)
- Designed to have improved flow properties and be suitable for direct compression process
- Manufactured by roller compaction of Carbopol 971P polymer

Carbopol® 971P NF Polymer (Powder)



Schematic representation of the manufacture of Carbopol® 71G NF polymer

Carbopol® 71G NF Polymer (Granular)

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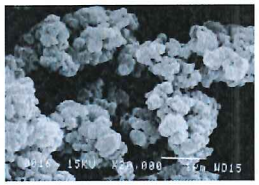
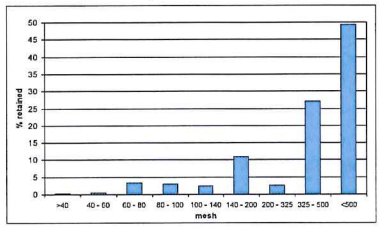
Carbopol® 971P NF Polymer → Carbopol® 71G NF Polymer

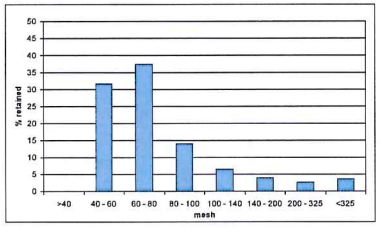


SEM of Carbopol® 971P NF polymer

SEM of Carbopol® 71G NF polymer



Typical particle size distribution of Carbopol® 971P NF polymer



Typical particle size distribution of Carbopol® 71G NF polymer

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Typical Properties of Carbopol® 71G NF Polymer

Property	Value Range
Bulk density (kg/m^3)	325 – 400
Tap density (kg/m^3)	400 - 465
BET surface area (m^2/g)	12 - 14

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Performance of Carbopol® 71G NF Polymer in Tablets – Inter-Lot Reproducibility

	Lot				
Properties	**#47**	**#48**	**#49**	**#50**	**#51**
Polymer					
Bulk density(g/cc)	0.362	0.366	0.363	0.368	0.373
Tap density(g/cc)	0.426	0.428	0.428	0.433	0.437
Hausner ratio	1.175	1.169	1.178	1.178	1.172
Compressibility index	14.91	14.43	15.14	15.08	14.66
Tablets					
Weight (mg)	303.00 ± 2.71	303.13 ± 2.04	303.98 ± 2.08	303.26 ± 2.43	304.37 ± 1.91
Thickness (mm)	4.27 ± 0.02	4.25 ± 0.02	4.25 ± 0.02	4.25 ± 0.01	4.24 ± 0.01
Hardness (kP)	10.31 ± 0.62	10.24 ± 0.90	10.93 ± 0.57	10.42 ± 0.68	10.80 ± 0.3
Friability (%)	0.08	0.07	0.10	0.07	0.12

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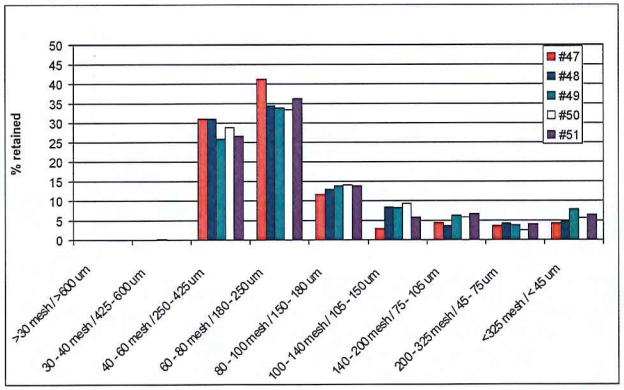
Polymers Formulation Manufacturing

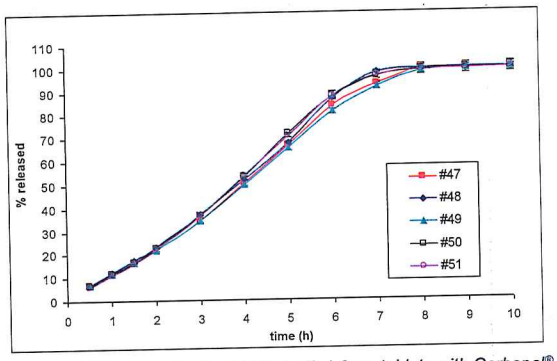
Performance of Carbopol® 71G NF Polymer in Tablets – Inter-Lot Reproducibility



Particle size distribution of Carbopol® 71G NF polymer

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Performance of Carbopol® 71G NF Polymer in Tablets – Inter-Lot Reproducibility



Theophylline release (USP apparatus 2, pH=7.5 buffer) from tablets with Carbopol® 71G NF polymer

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Carbopol® Polymers for Hydrophilic Matrix Tablets - Processing

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Benefits of Carbopol® 71G NF Polymer

- Good flow in high-speed equipment
- Good compressibility
- Minimal dust and static adherence
- Controlled release performance in tablets
- Can be combined with powder grade Carbopol® polymers or other controlled release excipients to improve flowability of the formulation and achieve flexibility in drug release performance
- Reproducibility
- Global pharmacopeial status, established master file with FDA and regulatory support for EU manufacturing authorizations

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Polymers Formulation Manufacturing

Manufacture of Tablets with Carbopol® Polymers

- Carbopol allows flexibility in choosing the processing method:
  - Wet granulation
  - Dry granulation
  - Direct compression
- By optimizing the formulation and process parameters, target tablet characteristics and drug release profiles can be achieved

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Polymers Formulation Manufacturing

Wet Granulation

- Direct compression is not feasible for matrix formulations containing high levels of powder Carbopol® polymers (>5% wt).
- Wet granulation can be used for powder grades of Carbopol polymers (971P NF, 974P NF) or Noveon AA-1 polycarbophil.
  - Typical usage levels are 5 - 10% wt polymer.
  - Polymer levels up to 20% wt may be processed by high shear granulation.
- Wet granulation is generally more efficient (lower polymer levels are necessary) than direct compression due to different surface area of the polymers used (powder vs. granular).

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Wet Granulation

For Aqueous Wet Granulation four factors must be controlled

(1) Amount of water

(2) Rate of water addition

(3) Mixing speed

(4) Wet massing time

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Amount of Water

- Amount of water should be 10 to 20 weight percent of the dry mix
- Amount should be tuned depending upon
  - Dry mix composition – water soluble v/s water insoluble ingredients
  - Mixing equipment efficiency – High shear is generally recommended over planetary or other low shear mixers

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Rate of water addition

- Water should be added gradually
  - As a thin stream
  - As droplets using peristaltic pump or
  - As a spray
- Water should not be added at once

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Mixing speed

- Mixing speed should be sufficiently high to enable fast and even water distribution to all the dry blend
- "Tip Speed" calculations should be performed to facilitate scale up
- Tip Speed = Circumference x RPM

for R&D scale high shear mixing (350 rpm)
Production scale low shear mixing (75 rpm).

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Wet Massing Time

- Wet massing time should be high to allow "In-situ Binder Activation"
  - After addition of water, the mass will look dry for about 1 to 2 minutes
  - Do not add additional water
  - Do not stop the mixing
  - Continue to mix and wet mass as small rounded wet granules will be formed

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the finer granules obtained from granulation is the better so it dries better.

Granulation Success

Before Drying

After Drying

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Wet Granulation – Processing Considerations

- The polymer should be incorporated in the powder blend (versus adding it as aqueous dispersion) due to the high viscosity of the polymer.
- Screening or combining the polymer with other ingredients is beneficial to improve dry polymer handling (compensates for static charge and fine particle size).
- No additional binder is required because Carbopol polymers have good binding properties.
- Granulation should be controlled in order to prevent over-wetting (sticky, rubbery mass).
- Incorporation of low levels of microcrystalline cellulose improves the processability of the formulation.
- It is very important to control the drying process and residual moisture in the granules (typical values 1 - 3%).
- Selection of container/closure system is essential for product stability (moisture permeation).

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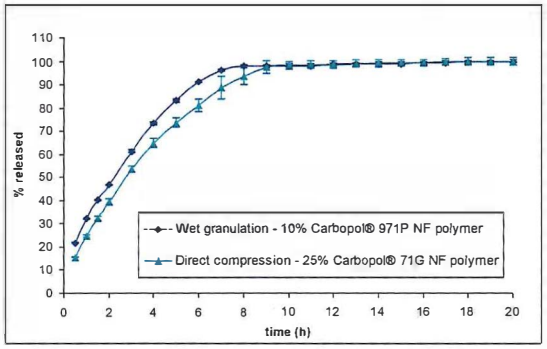
Wet Granulation



Effect of polymer type / manufacturing method on Theophylline release (apparatus 2, USP method for modified release)

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Polymers Formulation Manufacturing

High Shear Granulation – Formulations Containing 20% Carbopol® 971P NF Polymer

Objective: identify granulation conditions for extended release tablets with 20% Carbopol 971P NF polymer and different APIs: Guaifenesin – water soluble, Ketoprofen – low solubility.

Ingredient (% w/w)	Guaifenesin	Ketoprofen
Guaifenesin	75.00	-
Ketoprofen	-	66.66
Carbopol® 971P NF polymer	20.00	20.00
Emcocel® 50 microcrystalline cellulose	4.50	3.78
Lactose monohydrate	-	7.56
Talc	-	1.00
Cab-O-Sil® M5 fumed silica	-	0.50
Magnesium stearate	0.50	0.50
Total	*100*	*100*
Tablet weight (mg)	800	300

High shear granulation with deionized water in TMG Glatt machine; spraying rate and water amount adjusted for each API.

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Polymers Formulation Manufacturing

High Shear Granulation – Formulations Containing 20% Carbopol® 971P NF Polymer

	Guaifenesin	Ketoprofen
Dry mixing		
Speed (impeller / chopper) rpm	300/500	300/500
Mixing time (min.)	6	6
Spraying		
Speed (impeller / chopper) rpm	400/750	400/750
Spray rate (%w/w /min.)	1.29	3.66
Wet massing		
Speed (impeller / chopper) rpm	600/300	600/300
Time (min)	1.0	1.0
Total water added (%w/w)	5.0	17.5

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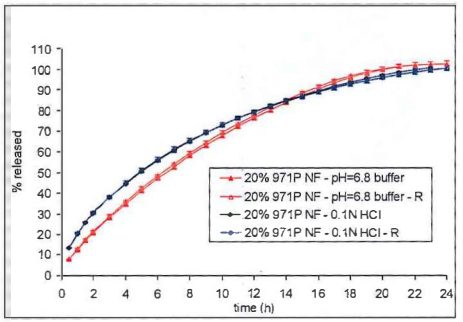
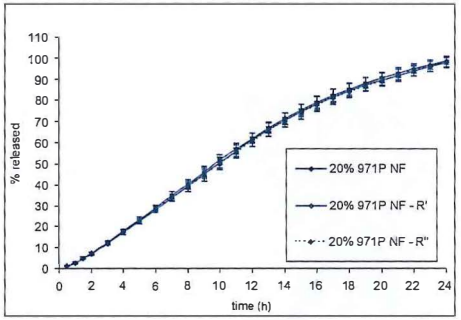
Polymers Formulation Manufacturing

High Shear Granulation – Formulations Containing 20% Carbopol® 971P NF Polymer



Guaifenesin release in pH=6.8 buffer or 0.1N HCl



Ketoprofen release in pH=6.8 buffer

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Polymers Formulation Manufacturing

High Shear Granulation – Formulations Containing 20% Carbopol® 971P NF Polymer

- Granulation conditions for formulations containing 20% 971P NF were different based on API solubility:
  - Guaifenesin - low water level (5%) and low water spray rate (7.69 g/min)
  - Ketoprofen - higher water level (17.5%) and higher spray-rate (21.72 g/min).
- Low solubility API requires stricter control of the conditions – more difficult to extrapolate to lower polymer levels (require higher amount of water).

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Polymers Formulation Manufacturing

Roller Compaction

- Roller compaction is an alternative granulation technology for formulations containing powder grades of Carbopol® polymers.
- It avoids rapid polymer swelling in water, that may make the wet granulation process difficult sometimes (especially at high levels of polymer).
- The blends of drug, Carbopol polymer, and other excipients (except the lubricant) are roller compacted and the resulting granules mixed with the lubricant and compressed.
- In some cases lower polymer levels are necessary for roller compaction than direct compression or wet granulation.

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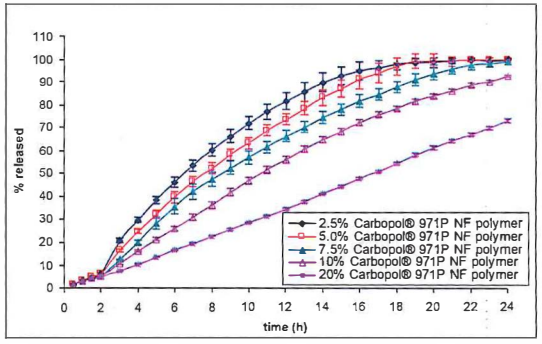
Polymers Formulation Manufacturing

Roller Compaction



Ketoprofen release (apparatus 2, USP method for modified release) from roller compacted tablets with Carbopol 971P NF polymer - Ketoprofen 50 mg tablets

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Direct Compression

- Powder grades of Carbopol polymers have good binding properties, but very fine particle size and static charge (thus not free flowing) – typical inclusion levels 3 – 5% wt.
- Carbopol 71G NF polymer:
  - Good flow and compressibility - forms tablets with excellent hardness and friability.
  - Usage level of 10 – 30% of the tablet weight can provide controlled release characteristics (depending on the drug properties and other formulation variables).
- Compression forces which result in acceptable hardness are not expected to significantly affect the drug release characteristics.

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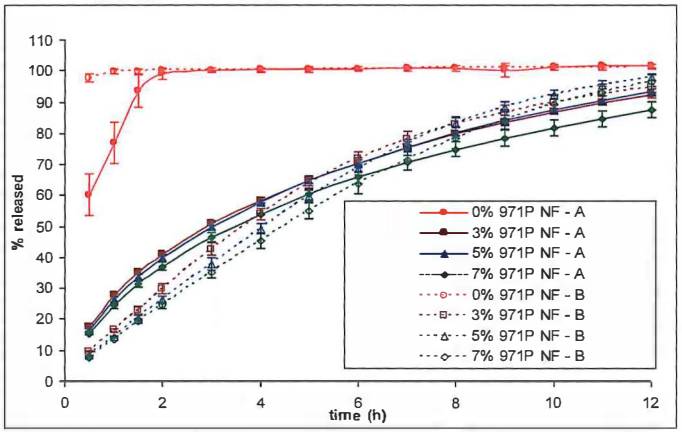
Polymers Formulation Manufacturing

Direct Compression

Powder grades of Carbopol polymers may provide some extended release properties even at low inclusion levels: 3 – 5% wt.



Caffeine release in 0.1N HCl (A) or pH=6.8 phosphate buffer (B) from tablets (200 mg)

Lubrizol

Designing Multiparticulates with Carbopol® Polymers

- Extrusion spheronisation
- Powder layering

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Extrusion Spheronization using Carbopol® Polymers

Manufacturing pellets with Carbopol polymers:

- In the presence of electrolytes (e.g. calcium chloride in the granulation fluid) – not recommended:
  - Easier processing by reducing the tackiness of the wet mass
  - Negative consequence on the bioadhesion and drug release
- Without the addition of electrolytes:
  - Bioadhesive or controlled release properties are maintained

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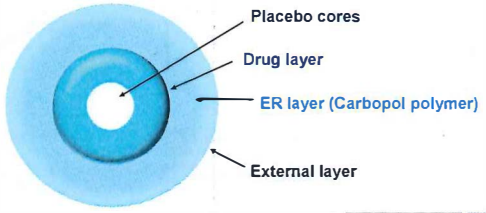
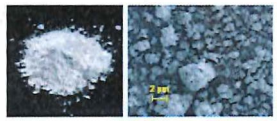
Polymers ormulation Manufacturing

Powder Layering using Carbopol® Polymers



Why Carbopol® polymer

- Very fine particle size (large surface area)
- Good binding properties
- Controlled release at low inclusion level
- Enables bioadhesive and/or extended release functionality
- Patentable technologies - product differentiation and/or life cycle extension



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Polymers Formulation Manufacturing

Powder Layered Pellets

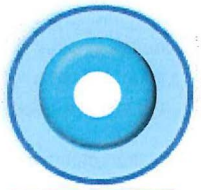
Domperidone
(50 % w/w) IR Pellets

Carbopol 971P NF (5 or 10%)
Talc
DCP or starch

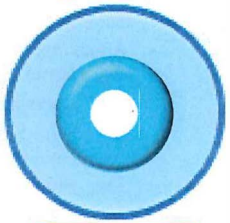
Binder HPMC E-5 (Pharmacoat 606)
(Spray)

Domperidone ER pellets

50% IR PELLETS
0.7- 0.8 mm



40% ER PELLETS
1.3 – 1.4 mm



20% ER PELLETS
1.7 - 1.8 mm

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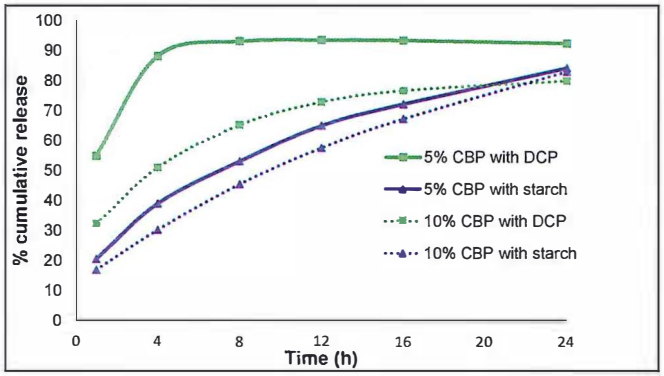
Polymers Formulation Manufacturing

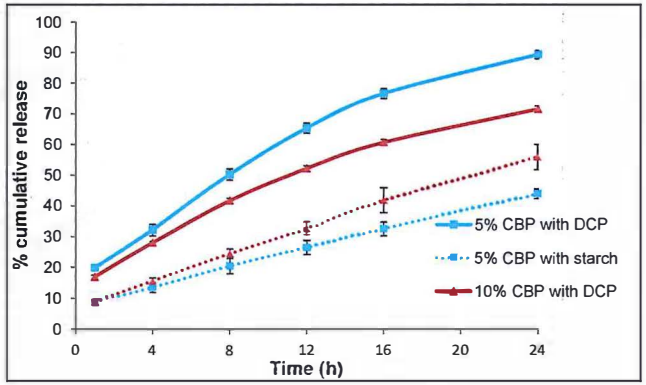
Domperidone 40% ER Pellets with Carbopol® Polymers



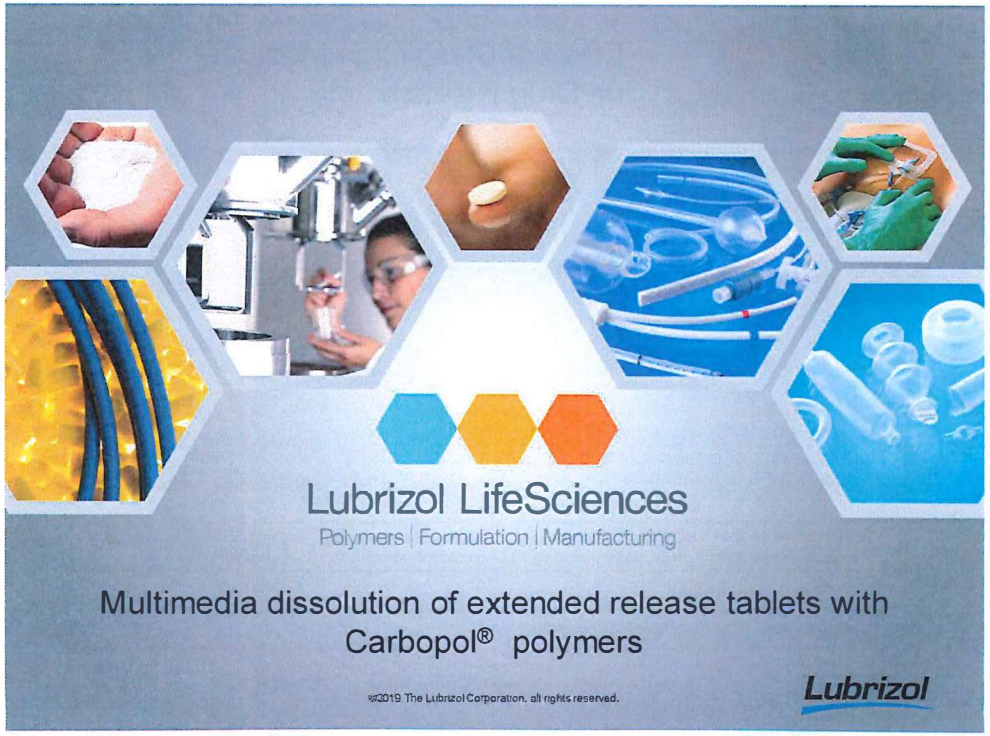
Pellets properties may be tailored by changing polymer level, coexcipient and layer thickness.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Domperidone 20% ER Pellets with Carbopol® Polymers



Pellets properties may be tailored by changing polymer level, coexcipient and layer thickness.



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Effect of Dissolution Medium on Drug Release

Reality

- Carbopol polymers are anionic.
- At lower pH values:
  - Gel formation occurs, even if the polymer is not fully swollen and there are larger regions of microviscosity (lower viscosity).
- As the pH increases:
  - The ionization of the carboxylic acid groups causes maximum swelling, resulting in fewer and smaller regions of microviscosity (higher viscosity).

Perception

- Drug release may be medium-dependent (the processes of swelling and gel formation are pH-dependent).
- At lower pH values:
  - the solvent can penetrate fast and deep into the glassy core and the drug is released faster, before complete gel formation occurs.
- As the pH increases:
  - the viscous gel acts as a barrier for the release of the drug, thus prolonging the release longer than at lower pH values.

No significant difference in release profiles due to dissolution medium in the case of robust formulations containing drugs with pH-independent solubility.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Effect of Dissolution Medium on Drug Release

Strategies for Multimedia Compliance of Extended Release Tablets with Carbopol® Polymers:

- Two highly soluble, high dose drugs with pH independent solubility evaluated: metformin hydrochloride (500 mg/tablet) and guaifenesin (600 mg/tablet).
- Extended release matrix tablets were manufactured with 10% and 20%Carbopol 971P NF polymer by aqueous granulation process.
- Additional formulations containing combinations of Carbopol polymers with other co-ingredients were evaluated in order to improve f2 factor.
  - Cellulosic polymers - hypromellose and carboxymethylcellulose sodium.
  - Non-cellulosic polymers -Eudragit® L100 55, Eudragit® RSPO and sodium alginate.
  - Buffers for modulation of micro-environmental pH – sodium citrate and citric acid.
  - Diluents - maize starch and dicalcium phosphate

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Effect of Dissolution Medium on Drug Release

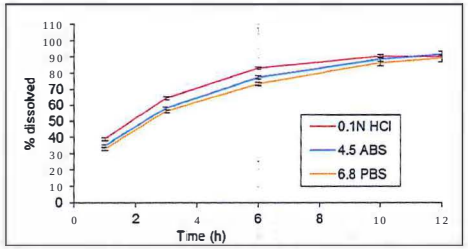
	Metformin			Guaifenesin		
Metformin hydrochloride	69	74	59	-	-	-
Guaifenesin	-	-	-	69	74	59
Carbomer homopolymer Type A (Carbopol 971P NF polymer)	20	20	20	20	20	20
Coexcipient	10 [a]	5 [b]	20 [c]	10 [a]	5 [b]	20 [c]
Colloidal silicon dioxide	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**
Tablet weight (mg)	***724.6***	***675.7***	***874.5***	***869.6***	***810.8***	***1016.9***

a -	- Hypromellose K100 LVCR, Hypromellose K4M, sodium CMC low viscosity, sodium CMC medium viscosity, sodium alginate low viscosity, sodium alginate high viscosity, Eudragit L100 55, Eudragit RSPO
b -	- Citric acid, sodium citrate
c -	- Maize starch, dicalcium phosphate dihydrate

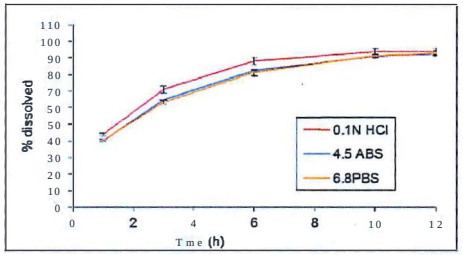
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Effect of Dissolution Medium on Drug Release

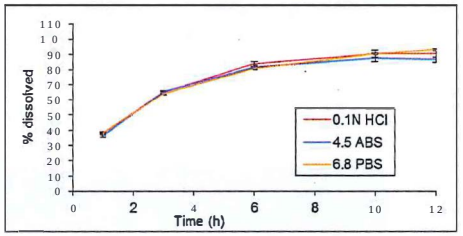
Multimedia dissolution compliance was achieved for **Metformin hydrochloride** extended release tablets formulated with combinations of:



Carbopol polymer and Hypromellose K100 LVCR (ratio 2:1)



Carbopol polymer and Hypromellose K4M (ratio 2:1)

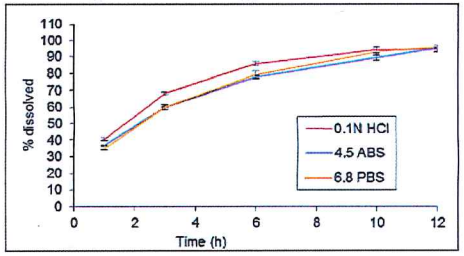


Carbopol polymer and Sodium CMC high viscosity (ratio 4:1)

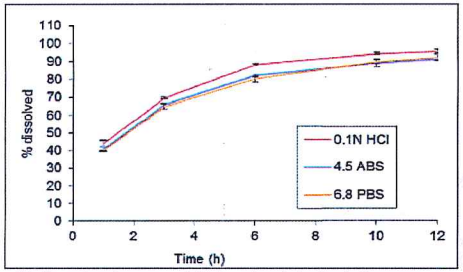
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Effect of Dissolution Medium on Drug Release

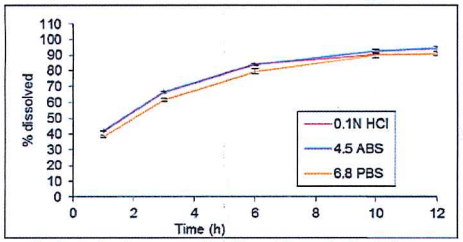
Multimedia dissolution compliance was achieved for **Metformin hydrochloride** extended release tablets formulated with combinations of:



Carbopol polymer and Sodium alginate low viscosity (ratio 2:1)



Carbopol polymer and Maize starch (ratio 1:1)



Carbopol polymer and Sodium citrate (ratio 4:1)

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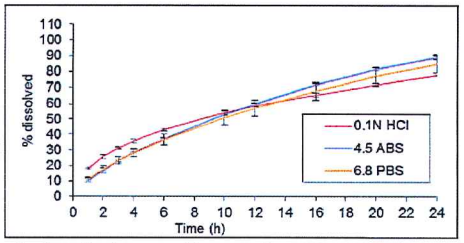
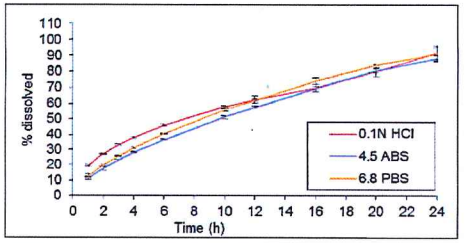
Polymers Formulation Manufacturing

Effect of Dissolution Medium on Drug Release

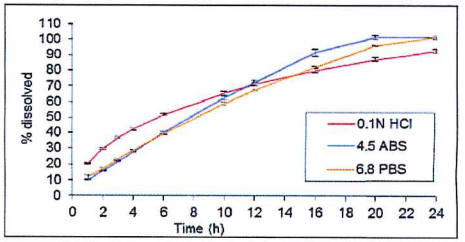
Multimedia dissolution compliance was achieved for **Guaifenesin** extended release tablets formulated with combinations of:



Carbopol polymer and hypromellose K100 LVCR (ratio 2:1)



Carbopol polymer and hypromellose K4M (ratio 2:1)



Carbopol polymer and Sodium alginate low viscosity (ratio 2:1)

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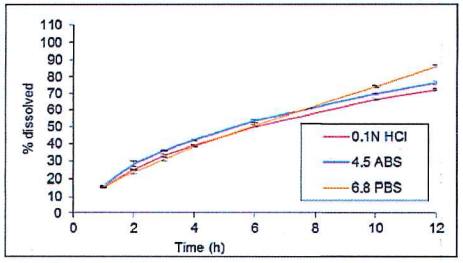
Polymers Formulation Manufacturing

Effect of Dissolution Medium on Drug Release

- Guaifenesin release from tablets formulated with 10% Carbopol polymer and 10% hypromellose K4M have shown f2 factor >50 in the three media.
- An alternative strategy of a porous enteric coating over matrix tablets was also successful in providing multimedia compliant release. The tablet cores containing 10% Carbopol polymer were coated with a porous enteric layer consisting of Eudragit L30D and hypromellose E6 (1:1) at 3% weight gain.



Guaifenesin tablets with 10% Carbopol polymer, coated with Eudragit L30D and hypromellose E6

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Polymers Formulation Manufacturing

Conclusion

- Carbopol® polymers may show pH dependent drug release, however, the multimedia dissolution can be matched to the desired f2 factor compliance by using several formulation techniques.
- Co – ingredients that helped to improve the F2 factor in case of Metformin HCl are Sodium CMC (Ceekol 100000), Hypromellose (HPMC K4M, HPMC K15M) Sodium alginate LV (Protanal® CR 8133), Hypromellose LV (Benecel® K100 LV), Sodium citrate/ Citric Acid
- Co – ingredients that helped to improve the F2 factor in case of Guaifenesin are Eudragit L30D and hypromellose (E6) permeable coat. Hypromellose (HPMC K4M, HPMC K15M)Sodium alginate LV (Protanal® CR 8133) Hypromellose LV (Benecel® K100 LV), Sodium CMC (Ceekol® 100000)

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Polymers Formulation Manufacturing

References:

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5. Al-Zoubi, N. M.; AlKhatib, H. S.; Obeidat, W. M., Evaluation of hydrophilic matrix tablets based on Carbopol® 971P and low-viscosity sodium alginate for pH-independent controlled drug release. Drug development and industrial pharmacy 2011, 37 (7), 798-808.
6. Joshi, N.; Ahmad, Z.; Mishra, S.; Singh, R., Formulation and evaluation of matrix tablet of Tramadol hydrochloride. Indian Journal of Pharmaceutical Education and Research 2011, 45 (4), 360-363.
7. Kotagale, N.; Patel, C.; Parkhe, A.; Khandelwal, H.; Taksande, J.; Umekar, M., Carbopol 934-sodium alginate-gelatin mucoadhesive ondansetron tablets for buccal delivery: Effect of PH modifiers. Indian journal of pharmaceutical sciences 2010, 72 (4), 471.

Lubrizol

Oral Solid Dose Formulations Containing Carbomers or Polycarbophil

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Polymers | Formulation | Manufacturing

APIs formulated as solid dosage forms with carbomers or polycarbophil

Acetyl cysteine	Diphenhydramine	Nifedipine *
Acetyl salicylic acid	Etodolac*	Nitrofurantoin*
Alfuzosin hydrochloride*	Fentanyl citrate	Pentoxifylline
Amfepramon hydrochoride*	Ferrous sulphate	Pramipexole*
Amlodipine	Furosemide	Pseudoephedrine*
Ascorbic acid	Galantamine*	Propranolol
Atenolol	Gingko biloba	Pyridostigmine bromide*
Atorvastatin calcium	Glucosamine	Pyridoxine chlorhydrate*
Buprenorphine	Guaifenesin*	Risperidone*
Bupropion	Indapamide*	Ropinirole*
Captopril	Isoniazid	Sodium fluoride
Carbamazepine	α - Lipoic acid	Sodium hyaluronate*
Cefixime	Lithium carbonate	Sodium valproate
Cefprozil	Loratadine	Tamsulosin hydrochloride*
Cetylpyridinium chloride*	Lorazepam	Testosterone*
Chlorpheniramine maleate	Magnesium lactate dihydrate*	Theophylline
Cloxacillin	Menthol*	Triamcinolone*
Dextromethorphan hydrobromide*	Mesalamine	Venlafaxine
Diclofenac	Metformin	Verapamil
Diethylpropion	Metixene	Viloxazine
	Metoprolol	Xanthan

(*) *denotes commercial products*

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U.S. – Solid Dosage Forms Containing Carbomers or Polycarbophil

Product	Company	Dosage Form	API	Excipients
Alfuzosin Hydrochloride ER Tablets	Aurobindo Pharma Limited	Tablet (ER)	Alfuzosin Hydrochloride 10 mg	**Carbomer homopolymer type B**, Silicon dioxide, Anhydrous dibasic calcium phosphate, Hydrogenated cottonseed oil, Hypromellose 2208, Hypromellose 2910, Magnesium stearate, Povidone K30, Propylene glycol, Titanium dioxide
Etodolac	TEVA Pharmaceuticals USA Inc.	Tablet (ER)	Etodolac 400 mg, 500 mg, or 600 mg	Anhydrous dibasic calcium phosphate, **Carbomer homopolymer type B**, Silicon dioxide, Hydroxypropyl cellulose, Hypromelloses, Lactose monohydrate, Magnesium stearate, Polyethylene glycols, Sodium lauryl sulfate, Titanium dioxide, D&C yellow #10, Aluminum oxide, FD&C red #40, FD&C yellow #6
Children's Mucinex® Chest Congestion mini-melts	Reckitt Benckiser LLC	Granules (orally disintegrating)	Guaifenesin 100 mg	Aspartame, Banana flavor, Butylated methacrylate copolymer, **Carbomer homopolymer type A**, Carboxymethylcellulose sodium, Magnesium stearate, Microcrystalline cellulose, Povidone, Sodium bicarbonate, Sorbitol, Stearic acid, Talc, Triethyl citrate, Tutti-frutti flavor

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U.S. – Solid Dosage Forms Containing Carbomers or Polycarbophil (Continued)

Product	Company	Dosage Form	API	Excipients
Children's Mucinex® Cough mini-melts	Reckitt Benckiser LLC	Granules (orally disintegrating)	Guaifenesin 100 mg; Dextromethorphan hydrobromide 5 mg	Aspartame, Butylated methacrylate copolymer, **Carbomer homopolymer type A**, Creme flavor, Magnesium stearate, Microcrystalline cellulose, Orange flavor, Povidone, Sodium bicarbonate, Sodium carboxymethylcellulose, Sorbitol, Stearic acid, Talc, Triethyl citrate
Mucinex®	Reckitt Benckiser LLC	Tablet (ER bi-layer)	Guaifenesin 600 or 1200 mg	**Carbomer 934P NF**, FD&C blue 1 aluminum lake, Hypromellose USP, Magnesium stearate NF, Microcrystalline cellulose NF, Sodium starch glycolate NF
Mucinex® DM	Reckitt Benckiser LLC	Tablet (ER bi-layer)	Guaifenesin 600 or 1200 mg; Dextrometorphan hydrobromide 30 or 60 mg	**Carbomer 934P NF**, FD&C yellow #10 aluminum lake, Hypromellose USP, Magnesium stearate NF, Microcrystalline cellulose NF, Sodium starch glycolate NF
Mucinex® D	Reckitt Benckiser LLC	Tablet (ER bi-layer)	Guaifenesin 600 or 1200 mg; Pseudoephedrine hydrochloride 60 or 120 mg	**Carbomer 934P NF**, D&C yellow #6, aluminum lake; Hypromellose USP, Magnesium stearate NF, Microcrystalline cellulose NF, Sodium starch glycolate NF.

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Polymers | Formulation | Manufacturing

U.S. – Solid Dosage Forms Containing Carbomers or Polycarbophil (Continued)

Product	Company	Dosage Form	API	Excipients
Macrobid®	Almatica Pharma Inc.	Capsule	Nitrofurantoin 100 mg	**Carbomer 934P**, Corn starch, Compressible sugar, D&C yellow #10, Edible gray ink, FD&C blue #1, FD&C red #40, Gelatin, Lactose, Magnesium stearate, Povidone, Talc, Titanium dioxide.
Mirapex ER®	Boehringer Ingelheim Pharmaceuticals, Inc.	Tablet (ER)	Pramipexole dihydrochloride monohydrate 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, or 4.5 mg	**Carbomer homopolymer type A**, Hypromellose, Corn starch, Colloidal silicon dioxide, Magnesium stearate
Risperdal® M-TAB	Janssen Pharmaceuticals, Inc.	Tablet (orally disintegrating)	Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg or 4 mg	Amberlite® resin, Gelatin, Mannitol, Glycine, Simethicone, **Carbomer**, Sodium hydroxide, Aspartame, Red ferric oxide, Peppermint oil (NOTE: 3 and 4 mg tablets contain xanthan)
Striant™ Mucoadhesive	Columbia Labs, Inc.	Buccal system (mucoadhesive tablet)	Testosterone 30 mg	Anhydrous lactose NF, **Carbomer 934P**, Hypromellose USP, Magnesium stearate NF, Lactose monohydrate NF, **Polycarbophil USP**, Colloidal silicon dioxide NF, Starch NF, Talc USP.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

U.S. – Solid Dosage Forms Containing Carbomers or Polycarbophil (Continued)

Product	Company	Dosage Form	API	Excipients
*Oramoist®	Quantum Health, Inc.	Buccal Tablet		Xylitol, Polyvinyl pyrrolidone, **Carbomer homopolymer type A**, Lemon flavor, Citric acid, Calcium carbonate, Hydroxy propyl cellulose, Triglycerides, Sodium choloride, Silicon dioxide, Magnesium stearate, Glucose oxidase, Lysozyme, Lactoferrin, Annatto
Metformin Hydrochloride	Aurobindo Pharma Limited	Tablet, Extended Release	Metformin hydrochloride	carbomer, isopropyl alcohol, hydroxy propyl cellulose, hypromellose, magnesium stearate, and microcrystalline cellulose.
*Canker Cover®	Quantum Health, Inc.	Buccal Tablet	Menthol 2.5 mg	**Carbomer 941**, Xylitol, Hydroxypropyl cellulose, Silicon dioxide, Carnallite,, Citrus oil, Annatto
Lyrica CR	Pfizer Inc.	CR tablets	Pregabalin	Cabomer, Kollidon SR (polyvinyl acetate, povidone, sodium lauryl suphate, and silica), crospovidone, polyethylene oxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol and colorants.

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Europe - Solid Dosage Forms Containing Carbomers or Polycarbophil

Product	Company	Dosage Form	API	Excipients
Tenuate® Retard	Artegodan	Tablets (ER)	Amfepramon-HCl 75 mg	Lactose, **Carbomer**, Zinkstearat, Weinsäure, Povidon
Farin Gola	Montefarmaco OTC SpA	Buccal Tablet	Cetylpyridinium chloride 1.2 mg	Saccarosio CD, Amido di mais, Aspartame, **Polycarbophil**, Povidone K30, Magnesio stearato, Talco, Aroma arancia, Aroma menta
Galnora SR	Krka, d.d.	Tablets filled into Gelatin Capsules	Galantamine 8, 16, or 24 mg	Lauril sulfato de sodio, Metacrilato de amonio Copolímero (tipo B), Hipromelosa, **Carbomero**, Hidroxipropil, Celulosa, Estearato de magnesio, Talco, Dióxido de titanio (E171), Tinta de impresión (shellac, Propilenglicol, Solución de amoniaco concentrado, Oxido de hierro Negro (E172), Hidróxido de potasio)

Lubrizol LifeSciences
Polymers | Formulation | Manufacturing

Europe- Solid Dosage Forms Containing Carbomers or Polycarbophil (Continued)

Product	Company	Dosage Form	API	Excipients
Indapen® SR	Polpharma Group	Tablet (SR)	Indapamide 1.5 mg	Laktoza jednowodna, **Karbomer**, Hydroksypropyloceluloza, Magnezu stearynian, Krzemionka koloidalna Bezwodna i talk, Stanowiące rdzeń tabletki, Oraz hypromeloza, Tytanu dwutlenek (E 171), Laktoza jednowodna, Makrogol 3000, Glicerolu trójoctan, Zelaza tlenek żółty (E172), Zelaza tlenek czerwony (E172) i żelaza tlenek czarny (E172)
Reducto®-spezial Dragees	Temmler Werke GmbH (Member of Aenova Group)	Coated Tablets	Disodium hydrogen phosphate 2-H_2O 360 mg; Hydrogen phosphate ion 19412.8 mg; Potassium 172.96 mg; Potassium dihydrogen phosphate 602 mg; Sodium ion 93 mg	Carmellose-Natrium, **Carbomer**, Dibutylphthalat, Wachs, Magnesiumstearat, Poly(methacrylsäure,methylmethacrylat), Siliciumdioxid, Talkum, Farbstoff Titandioxid (E 171)
Magné B6®	Sanofi	Coated Tablets	Magnésium lactate dihydrate 470 mg; Pyridoxine chlorhydrate 5 mg	Saccharose, Kaolin lourd, Gomme arabique, **Carbomère**, Talc, Magnésium stéarate, Titane dioxyde, Cire de carnauba

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Europe - Solid Dosage Forms Containing Carbomers or Polycarbophil (Continued)

Product	Company	Dosage Form	API	Excipients
SR Nifedipine	Valpharma International SpA	Tablet	Nifedipine 30 mg or 60 mg	Talco, Povidone, Lattosio monoidrato, **Carbomer 974P**, Ipromellosa, Silice, Colloidale anidra, Magnesio stearate, Polimetacrilato basico (Eudragit E), Titanio diossido (E171), Ossido, Ferrico (E172), Macrogol 4000
Sifrol® Retardtabletten	Boehringer Ingelheim PTY Limited	Tablets (ER)	Pramipexole hydrochloride 0.125 mg, 0.25 mg, 1 mg, or 1.5 mg	Hypromellose 2208, Maisstärke, **Carbomer 941**, Hochdisperses siliciumdioxid, Magnesiumstearat
Kalymin®	Temmler Werke GmbH (Member of Aenova Group)	Tablet	Pyridostigmine bromide 180 mg	Glutaminsäure hydrochlorid, Siliciumdioxid (gefällt), Calciumhydrogenphosphat, Siliciumdioxid (hochdisperses), **Carbomer**, Magnesium stearat
Risperdal® - QUICKLET®	Janssen-Cilag Pty Limited	Tablets (IR)	Risperidone 0.5, 1, 2, 3, or 4 mg	Polacrilex harz (methacrylsäure-polymer m. divinylbenzen), Gelatine, Mannitol, Glycin, Simeticon, **Carbomere**, Natriumhydroxid, Aspartam, E 172, Pfefferminzöl -2 mg/-3 mg/-4 mg zusätzl.: Xanthangummi

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Europe- Solid Dosage Forms Containing Carbomers or Polycarbophil (Continued)

Product	Company	Dosage Form	API	Excipients
Rolpryna SR	Krka, d.d.	Tablet	Ropinirole 2 mg, 4 mg, or 8 mg	Hypromellose type 2208, Lactose monohydrate, Colloidal anhydrous silica, **Carbomer**, Hydrogenated castor oil, Magnesium stearate, Hypromellose type 2910, Titanium dioxide (E171), Macrogol 400, Red iron oxide (E172), Yellow iron oxide (E172); 4 mg and 8 mg includes Black iron oxide (E172)
Tamnexyl XL	Clonmel Healthcare Ltd	Tablet	Tamsulosin hydrochloride 0.4 mg	Cellulose microcrystalline, Hypromellose, **Carbomer**, Silica colloidal anhydrous
Aftab®	Rottapharm Madaus GmbH	Buccal tablet	Triamcinolonacetonid 0.025 mg.	Hyprolose, **Carbomer**, Magnesiumstearat, Talkum, Aluminiummagnesiumsilicat (2:1:2), Lactose 1H2O, Carmellose-Calcium, Gelborange S (E 110)

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Europe- Solid Dosage Forms Containing Carbomers or Polycarbophil (Continued)

Product	Company	Dosage Form	API	Excipients
GeloRevoice®	Pohl-Boskamp GmbH & Co. KG	Lozenge	Sodium hyaluronate, **Carbomer**, Xanthan	Mannitol, Natriumhydrogencarbonat, Xylitol, Citronensäure, Macrogol, Aspartam, Aromen, Kaliumhydrogenphosphat, Zinkstearat, Siliciumdioxid
Cevitt® Hals & Rachen Lutschtabletten	HERMES MEDICINAL GmbH	Buccal Tablet	Sodium hyaluronate, Xanthan, **Carbomer**	Mannitol, Natriumhydrogencarbonat, Sorbitol, Citronensäure, Aspartam, Vitamin C, Aroma, Zinkcitrat Dihydrat

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Polymers Formulation Manufacturing

Conclusions

Lubrizol pharmaceutical polymers provide key benefits in oral solid dosage forms:

- **Efficiency** (low total polymer level)
  - Enables smaller tablet size
  - Overall formulation cost savings
- **Processing versatility**
  - Ability to choose various manufacturing technologies
  - Availability of powder and granular forms
- **Flexibility**
  - In modulating drug release
  - In formulation: actives with different properties can be formulated to achieve various extended release profiles
- **Development of intellectual property**
  - Patentable technologies that offer the benefits of product differentiation and/or life cycle extension

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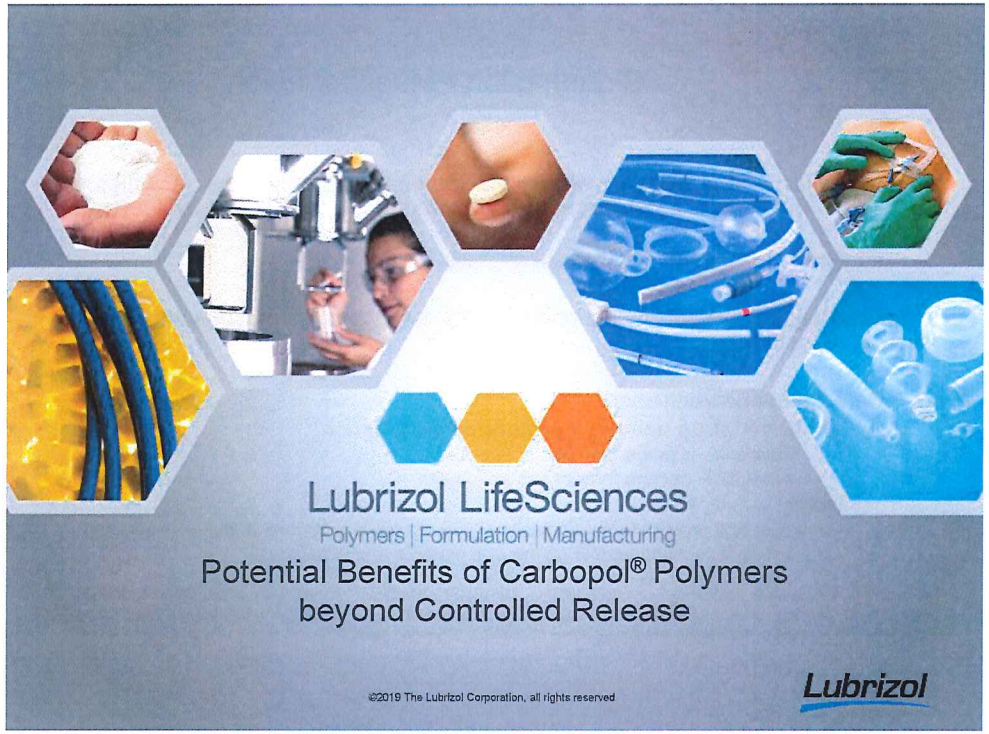

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Potential Benefits of Carbopol® Polymers beyond Controlled Release

- Bioadhesion
- Suspending agent (freeze drying)
- Control of microenvironmental pH
- Taste masking
- Inhibition of proteolytic enzymes
- Gastric floating systems

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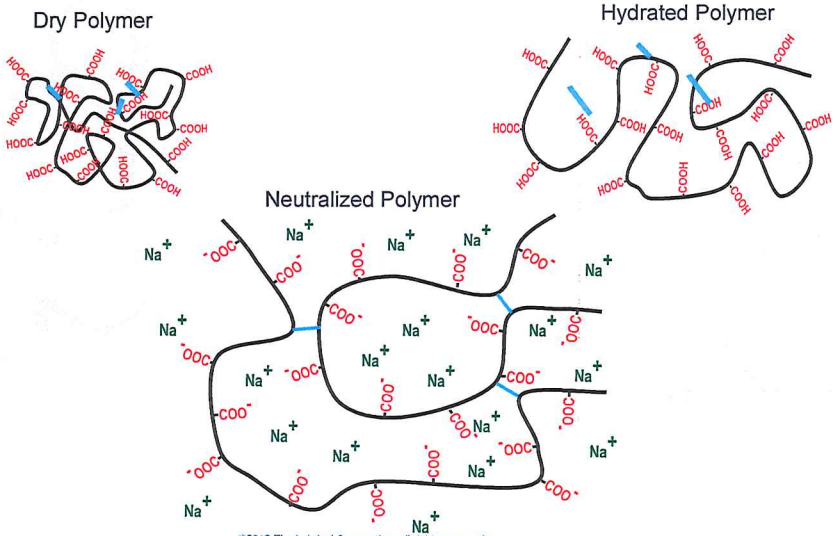
Carbopol® Polymers Swelling Mechanism



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Mucoadhesive Properties of Carbopol® Polymers, Pemulen™ Polymers and Noveon® Polycarbophil

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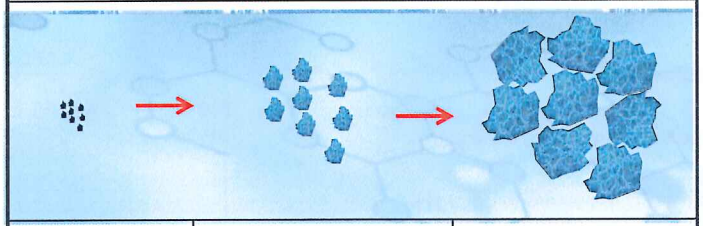
Carbopol® Polymer Swelling Mechanism

Dry Polymer	Hydrated Polymer	Neutralized Polymer
		
Ø = 2 - 7µm	pH = 3.0	Ø = 20- 70µm pH = 7.0

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Bioadhesion / Mucoadhesion

Bioadhesion - the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces.

- May have positive or detrimental aspects

Mucoadhesion - two surfaces, one of which is mucus or a mucous membrane, adhere to each other.

- Benefits of mucoadhesion:
  - **enhanced drug delivery / prolonged drug action**
    - localised – dosage form at site of action
    - systemic – dosage form at absorption site
  - **other**:
    - coat and protect damaged tissues (gastric ulcers or lesions of the oral mucosa)
    - act as lubricating agents (in the oral cavity, eye and vagina).

The basics and underlying mechanisms of mucoadhesion . Smart. JD., Adv Drug Deliv Reviews, 2005, 57(11):1556–68
Mucoadhesive polymeric platforms for controlled drug delivery. Andrews GP et al., Eur J Pharm Biopharm. 2009, 71(3):505-18.
Bioadhesion – a review of concepts and applications. Palacio MLB, Bhushan B. Phil. Trans. R. Soc. A 2012, 370:2321-47

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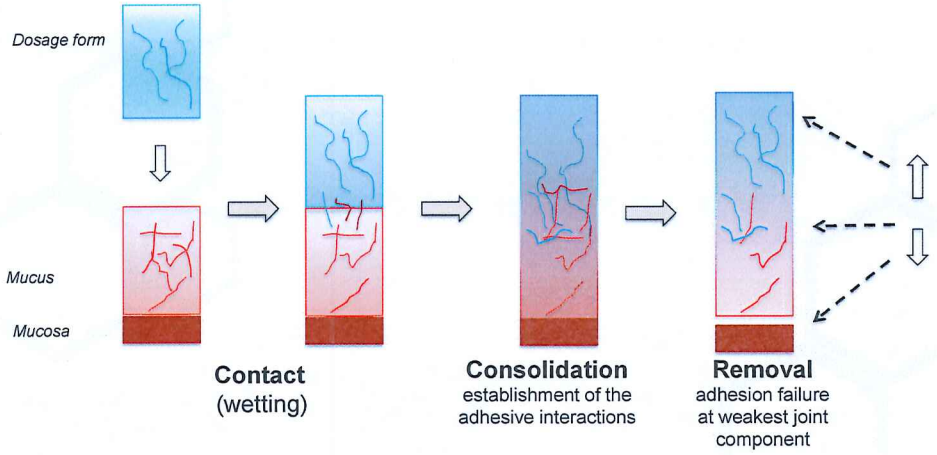
Polymers Formulation Manufacturing

Bioadhesion/Mucoadhesion Mechanism

Mucoadhesion - two surfaces, one of which is mucus or a mucous membrane, adhere to each other.



Mucoadhesion - complex scenario and mechanism

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Carbopol® Polymers – Mucoadhesion Mechanism

- Wetting - fast hydration of Carbopol® polymers allows the dosage forms to quickly establish the contact with the mucus upon administration.

- Consolidation of the adhesion:
  - **hydrogen bonding** - Carbopol polymers, having large amount of carboxylic groups, can establish hydrogen bonding with the mucus.
    This occurs when the polymer is used "as is", without neutralization - solid dosage forms (granules, tablets), anhydrous systems, etc.

  - **macromolecular penetration** - Carbopol® polymers in neutralized form are swollen to the largest extent and can interpenetrate with the glycoprotein chains from mucus, to form a network.
    This occurs when the polymer is neutralized - liquid or semisolid dosage forms containing buffers or bases.

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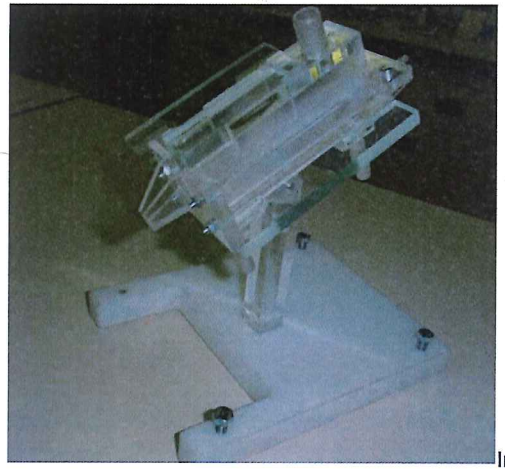
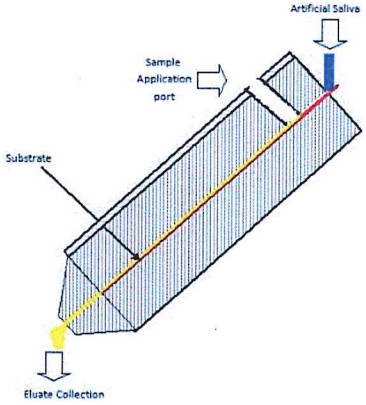
Mucoadhesion - In vitro Evaluation of Carbopol® Polymers

- Objective: evaluate in vitro mucoadhesive properties of Carbopol® polymers, in comparison with other excipients





In Vitro Oesophageal Retention Model (IVOR)
Modified from Young and Smart, J Pharm Pharmacol. (1998), 50, 167

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Polymers Formulation Manufacturing

Experimental Design

Study design	Criteria	Parameters
Materials (samples)	Suitable for oral care applications	Carbopol® polymers • 974P NF (Carbomer homopolymer type B) • 971P NF (Carbomer homopolymer type A) • ETD 2020 NF (Carbomer interpolymer type B)
		Other polymers: • Sodium carboxymethyl cellulose (9M31F) • Hydroxypropyl cellulose (MW 80,000) • Xanthan gum (Keldent®) • Carrageenan (Genuvisco® TPC-1) • PVM/MA copolymer (Gantrez® S-97 BF polymer) • Poloxamer (Kolliphor® P407)

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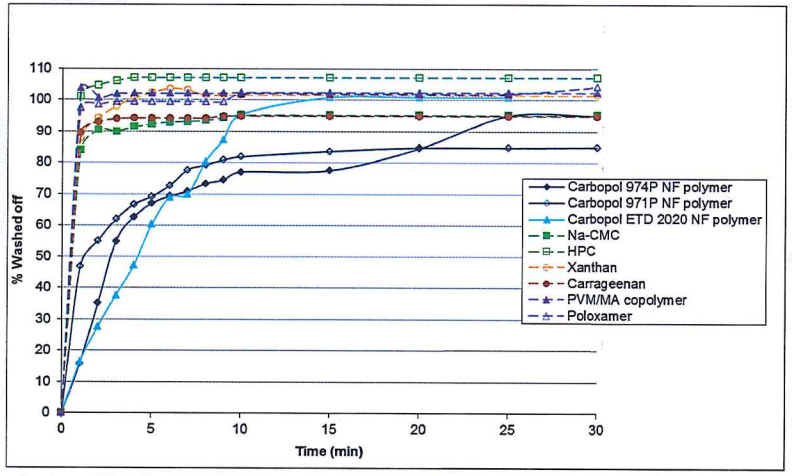
Polymers Formulation Manufacturing

In vitro Evaluation of 0.25% Dispersions



Carbopol® polymers provided better retention than other materials, which eluted >80% within 1 min.

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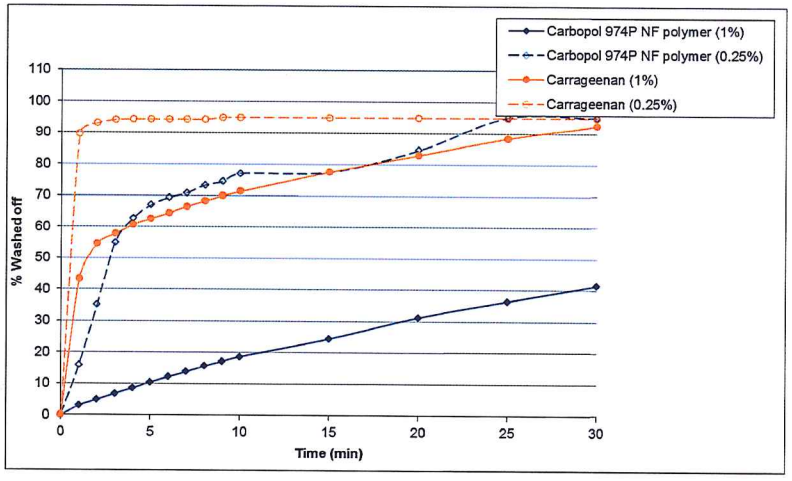
Effect of Concentration on Elution



Longer retention was achieved for the more concentrated dispersions.

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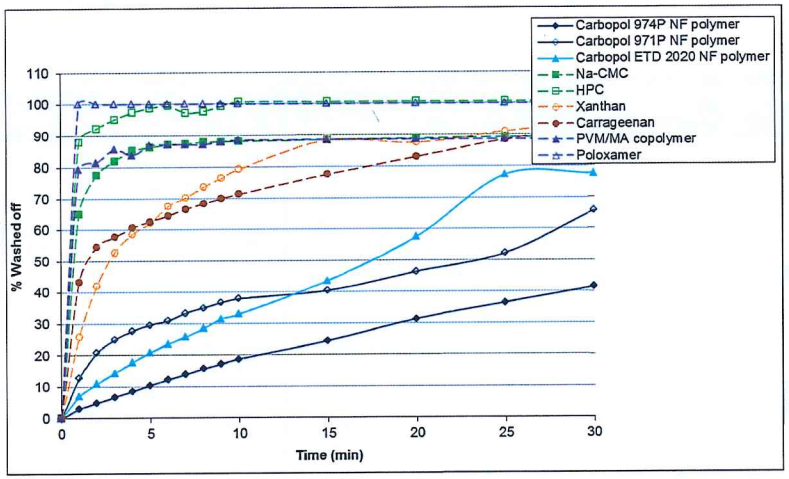
In vitro Evaluation of 1% Dispersions



Carbopol® polymers provided the longest retention (lower amount eluted), followed by carrageenan and xanthan.

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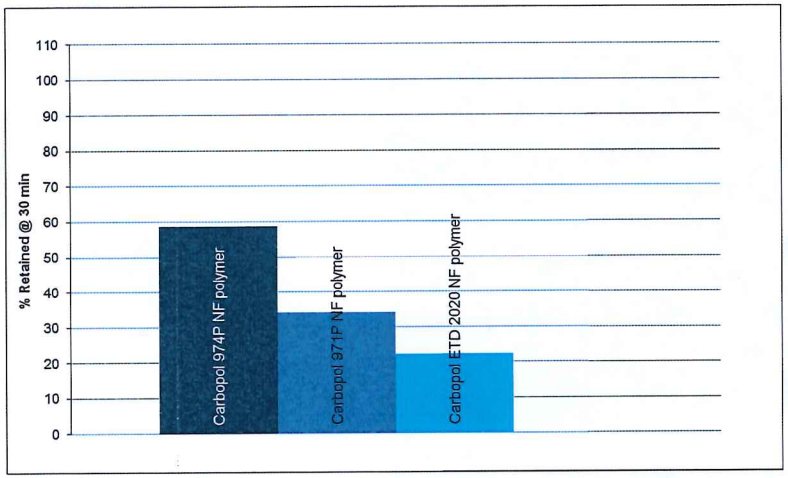
Polymers Formulation Manufacturing

Retention of Dispersions (1%) of Carbopol® Polymers After 30 Minutes



Results indicated retention for more than 30 minutes for Carbopol® polymers.

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Polymers Formulation Manufacturing

Mucoadhesion - In vitro Evaluation of Carbopol® Polymers

- In vitro evaluation of mucoadhesive properties indicated longer retention for Carbopol® polymers compared to other materials evaluated:
  - The advantage was observed both at 0.25 and 1% concentrations.
  - At 0.25% inclusion level, only Carbopol® polymers were retained, all other materials were washed off after 1 minute.
  - Longer retention was achieved for the more concentrated dispersions.
  - At 1% concentration, Carbopol® polymers provided the longest retention (lower amount eluted), followed by carrageenan and xanthan. Results indicated retention for more than 30 min for Carbopol® polymers.

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Applications of Mucoadhesive Properties of Carbopol® Polymers, Pemulen™ Polymers and Noveon® Polycarbophil

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Mucoadhesion Benefits

- **Enhanced drug delivery** by retaining a dosage form at:
  - the site of action – **localized drug delivery;** ex: leuprolide acetate, triamcinolone acetonid, mesalamine, menthol, nystatin, lidocaine, 5-fluorouracil, etc. Target mucosa included oral, colonic, rectal, ophthalmic, vaginal, etc.
  - the site of absorption – **systemic drug delivery**; ex: testosterone, nifedipine, morphine, fentanyl citrate, doxycycline, buprenorphine, etc.

- Other **therapeutic advantages**, by:
  - coating and protecting damaged tissues (gastric ulcers or lesions of the oral mucosa)
  - acting as lubricating agents (in the oral cavity, eye and vagina).

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Polymers Formulation Manufacturing

Mucoadhesion Benefits

Other advantages of oral mucoadhesion

- Carbopol® polymer was used to formulate mucoadhesive gels for localized treatment of xerostomia, and to help enhance the residence time of the product.
  Deasy et al., Int. J. Pharm (2004), 278: 391-406

- In-vitro adhesion to buccal mucosa (as demonstrated by isolation of buccal cells) was correlated to in-vivo adhesion. In-vivo administration as a mouthwash demonstrated the polymers persisted for at least 1 hour.
  Kockisch et al., J Control Release (2001), 77(1-2), 1-6

- Zinc cation complexed with Carbopol® 971P NF polymer, extended delivery of zinc locally within the oral cavity and sustained the antimicrobial effect. Zinc/Carbopol® Polymer complexes had similar bioadhesive properties to the polymer alone when tested with the buccal cell absorption model.
  J Smart et al., Intl. J Pharm (2007) 340: 92–96.

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Polymers Formulation Manufacturing

Mucoadhesion Benefits

Enhanced delivery - oral cavity:

- *Development and in vitro/in vivo evaluations of bioadhesive buccal tablets for nicotine replacement therapy. Ikinci et al., Pharmazie (2006), 61(3), 203-207*
- *Influence of compression force on the behavior of mucoadhesive buccal tablets. Perioli et al., AAPS PharmSciTech. 2008, 9(1), 274-281*
- *Formulation and in vitro-in vivo evaluation of buccoadhesive morphine sulfate tablets. Anlar et al., Pharm Res. (1994), 11(2), 231-236*
- *Development and characterization of buccoadhesive nifedipine tablets. Varshosaz et al., Eur J Pharm Biopharm. (2002), 54(2), 135-141*

Enhanced delivery - colon:

- *Design and evaluation of matrices of Eudragit with polycarbophil and carbopol® for colon-specific delivery. Asghar et al., J Drug Target. (2008), 16(10), 741-757*
- *The use of the InteliSite® Companion device to deliver mucoadhesive polymers to the dog colon. McGirr et al., Eur J Pharm Sci. (2008) Nov 21*
- *Novel combinations of rate-controlling polymers for the release of leuprolide acetate in the colon. Prabhu et al., Drug Deliv. (2008), 15(2), 119-125*
- *An oral formulation of nicotine for release and absorption in the colon: its development and pharmacokinetics. Green et al., Br J Clin Pharmacol. (1999), 48(4), 485-493.*

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Polymers Formulation Manufacturing

Examples of Mucoadhesive Commercial Products

Product	Active	Ingredients
Buccal Systems		
Onsolis® fentanyl buccal soluble film	Fentanyl citrate	Carboxymethylcellulose, citric acid, hydroxyethyl cellulose, hydroxypropyl cellulose, methylparaben, monobasic sodium phosphate, peppermint oil, **Polycarbophil**, propylene glycol, propylparaben, red iron oxide, sodium benzoate, sodium hydroxide, sodium saccharin, titanium dioxide, tribasic sodium phosphate, vitamin E acetate, water.
Striant® (testosterone buccal system) mucoadhesive	Testosterone	Anhydrous lactose, **Carbomer 934P**, hypromellose, magnesium stearate, lactose monohydrate, Polycarbophil, colloidal silicon dioxide, starch and talc
Aftab® tablets	Triamcinolon-acetonid	Hyprolose, **Carbomer**, Magnesiumstearat, Talkum, Aluminiummagnesiumsilicat (2:1:2), Lactose 1H2O, Carmellose-Calcium, Gelborange S (E 110).
Canker Cover® Canker Sore Patch	Menthol	**Carbomer homopolymer Type A**, polyvinyl pyrrolidone, xylitol, hydroxypropyl cellulose, Silicon dioxide, carnallite TM (mineral salt), Citrus oil, annatto.
OraMoist® Dry Mouth Relief Patch	-	Xylitol, Polyvinylpyrrolidone, **Carbomer Homopolymer**, Triglyceride, Lemon Flavor, Citric Acid, Calcium Carbonate, Hydroxypropyl Cellulose, Sodium Chloride, Silicone Dioxide, Magnesium Stearate, Glucose Oxidase, Lysozyme, Lactoferrin, Carmine CI 75470.

Trademarked products include Onsolis (BioDelivery Sciences International), Striant (Columbia Laboratories), Aftab (Meda Pharma), Canker Cover and OraMoist (Quantum), GeloRevoice (Pohl-Boskamp), Cevitt Hals & Rachen (Hermes Arzneimittel), Neo-Angin (Klosterfrau Healthcare Group), Isla (Engelhard Arzneimittel), MuGard (Abeona Therapeutics), Liquivisc (Thea Pharmaceuticals) Viscotears (Novartis), Crinone (Allergan), Hyalo Gyn (Fidia Pharma USA), and Replens and RepHresh (Church & Dwight)

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Examples of Mucoadhesive Commercial Products

Product	Active	Ingredients
Lozenges		
GeloRevoice® Throat Lozenges	Sodium hyaluronate, carbomer, xanthan	mannitol, sodium hydrogen carbonate, xylitol, citric acid, macrogol, aspartame, flavour (cherry, menthol), potassium monohydrogen phosphate, zinc stearate, silica.
Cevitt® Hals & Rachen	Sodium hyaluronate, carbomer, xanthan	Mannitol, sodium hydrogencarbonate, sorbitol, citric acid, aspartam, vitamin C, flavor, zinc citrate dihydrate.
neo-angin® stimmig Plus Lutschtabletten	-	**Carbopol®**, carrageenan, sodium hyaluronate, mannitol, sodium hydrogencarbonat, citric acid, macrogol, sucralose, cherry flavor, levomenthol, potassium monohydrogenphosphate, zinc stearate, silica, sorbitol, xanthan, flavor
isla® med hydro+ Pastillen	Extract of Cetraria Islandica, Carbomer, xanthan, sodium hyaluronate	Arabic gum, sorbitol, maltitol, anhydrous citric acid, potassium acesulfame, levomenthol, peppermint oil, anise, bitter fennel oil , medium chain triglycerides, purified water
Mouth rinse		
MuGard® Oral Mucoadhesive	-	Purified water, glycerin, benzyl alcohol, sodium saccharin, **carbomer homopolymer A**, potassium hydroxide, citric acid, polysorbate 60 and phosphoric acid.

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Examples of Mucoadhesive Commercial Products

Product	Active	Ingredients
Ophthalmic		
LIQUIVISC™ 2.5 mg/g, eye gel	Carbomer 974P	Benzalkonium chloride, Sorbitol, Lysine monohydrate, Sodium acetate trihydrate, Polyvinyl alcohol, Water for injections
Viscotears® Liquid Gel	Carbomer (polyacrylic acid)	Cetrimide, sodium hydroxide, sorbitol and water for injections
Viscotears® Single Dose Unit 2.0mg/g Eye Gel	Carbomer (polyacrylic acid)	Sorbitol, sodium hydroxide and water for injections
Vaginal		
Crinone® 8% w/w Progesterone Vaginal Gel	Progesterone	Glycerin, Light Paraffin, Hydrogenated Palm Oil Glyceride, **Carbopol® 974P**, Sorbic acid, **Polycarbophil**, Sodium hydroxide, Purified water
HYALO GYN® Vaginal Hydrating Gel	Hydeal-D® (hyaluronic acid derivative)	Propylene glycol, **carbomer (Carbopol® 974P)**, methyl p-hydroxy-benzoate, propyl p-hydroxybenzoate, sodium hydroxide, and purified water
Replens™ Vaginal Moisturizer	-	**Carbomer 934P**, glycerin, hydrogenated palm oil glyceride, mineral oil, **polycarbophil**, purified water and sorbic acid
RepHresh™ Vaginal Gel	-	Water, glycerin, **polycarbophil, carbomer homopolymer type B,** ethylparaben sodium, methylparaben sodium, propylparaben sodium, sodium hydroxide

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Potential Benefits of Carbopol® Polymers beyond Controlled Release

- Bioadhesion
- Suspending agent (freeze drying)
- Control of microenvironmental pH
- Taste masking
- Inhibition of proteolytic enzymes
- Gastric floating systems

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Control of Microenvironmental pH

- Weak basic drugs generally exhibit a drop in aqueous solubility with increasing pH, which may result in faster release in acidic media and slower/incomplete release in neutral or basic media.
- Carbomers are acidic materials (pH of the dispersion = 2.5 – 3.5).
- The acidic microenvironmental pH created by carbomers maintains the cationic drugs in a soluble form and help achieve a constant release rate over the gastrointestinal tract.
- Examples: Papaverine hydrochloride, Verapamil hydrochloride

- *Influence of Methacrylic and Acrylic Acid Polymers on the Release Performance of Weakly Basic Drugs from Sustained Release Hydrophilic Matrices. Tatavarti et al., J. Pharm. Sci. (2004), 93(9), 2319-2331*

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Taste Masking

- Taste making of some bitter APIs (mostly cationic drugs):
  - form insoluble adsorbates through weak ionic bonding
  - adsorbates dissolve rapidly after ingestion
  - Ex: macrolide antibiotics, enrofloxacin, dextromethorphan, fexofenadine, etc
  - US 4808411 A, US 5919489 A, WO 2009024535 A1, US 20030170310A1
- Use in combination with film-forming materials for taste-masking coating compositions to form "a soft, smooth, but mechanically stable surface perceived as pleasant in the mouth within seconds" for easy swallowing
  - *US 20080063713 A1*
- Carbopol polymers have been reported to ameliorate the throat catch (unpleasant taste and sensation in the throat) caused by ibuprofen.
  - Possible mechanisms: binding to specific sites in the throat or coating the mucosa to prevent contact of the bitter and/ or throat catch producing agent with the mouth and throat mucosa.
  - *US2007122475A1*

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Gastric Floating Systems

- Carbomers do not dissolve and are not metabolized in the gastrointestinal tract.
- In gastric medium, the polymers hydrate and swell, enabling floating.
- Carbomers can be used alone or in combinations with other polymers or effervescent systems to formulate gastric floating dosage forms.

- *Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers. Xu et al. Int. J. Pharm. (2006), 310, 139–145.*
- *Development of a Novel Controlled-Release System for Gastric Retention. Deshpande et al. Pharm. Res. (1997), 14(6), 815-819.*
- *Effect of Added Pharmatose DCL11 on the Sustained-Release of Metronidazole From Methocel K4M and Carbopol 971P NF Floating Matrices. Cedillo-Ramírez et al. Drug Dev. Ind. Pharm. (2006), 32(8), 955 – 965.*
- *Effect of Formulation and Process Variables on the Release Behavior of Amoxicillin Matrix Tablets. Tapia-Albarran et al., Drug Dev. Ind. Pharm. (2004), 30(8), 901 – 908.*

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Inhibition of Proteolytic Enzymes

- Polyacrylates may protect peptide drugs against enzymatic degradation by reversibly inhibiting the activity of α-chymotrypsin, trypsin, carboxypeptidase-A (binding of bivalent ions Ca, Zn / formation of a complex with the enzyme).

- *Direct interaction between a human digestive protease and the mucoadhesive poly(acrylic acid). Pallares et al., Acta Crystallogr D Biol Crystallogr. (2008), 64(7),784-791.*
- *Protective Effect of Carbopol on Enzymatic Degradation of a Peptide-Like Substrate I: Effect of Various Concentrations and Grades of Carbopol and Other Reaction Variables on Trypsin Activity. Vaidya et al., Pharm Dev. Techol (2007), 12, 89-96.*
- *Novel peroral dosage forms with protease inhibitory activities. II. Design of fast dissolving poly(acrylate) and controlled drug-releasing capsule formulations with trypsin inhibiting properties. Akiyama et al. Int. J. Pharm (1996), 138(1), 13-23.*
- *Mucoadhesive polymers in peroral peptide drug delivery. I. Influence of mucoadhesive excipients on the proteolytic activity of intestinal enzymes Lueßen et al., Eur. J. Pharm. Sci. (1996), 4(2), 117-128.*

- Polyacrylates can enhance the paracellular permeability of mucosal epithelia (intestinal, nasal) by transiently opening the tight junctions, thereby increasing the paracellular absorption of hydrophilic and macromolecular drugs.

- *Macromolecules as safe penetration enhancers for hydrophilic drugs—a fiction? Junginger et al., Pharm. Sci. & Technol. Today (1998), 1(9), 370-376.*
- *Carbopol-mediated paracellular transport enhancement in Calu-3 cell layers, Li et al., J Pharm Sci. (2006), 95(2),326-35.*

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Hot Met Extrusion

Sr. No.	Polymer Attribute	Details
1	Polymers recommended for HME	Carbopol 971P NF, Carbopol 974P NF, Carbopol 71G NF and Noveon AA-1 Polycarbophil USP
2	Glass Transition temperature	About 115^{0}C (Tg reduces with increase in LOD of polymer)
3	Heat Stability	Inhouse studies did not show changes in IR till 150^{0}C
4	Plasticizer	Triethyl Citrate
5	Recommended concentration	5 to 50 % along with other thermoplastic materials and depending upon MFI of resultant mixture

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Hot Melt Extrusion

Following are few references on HME

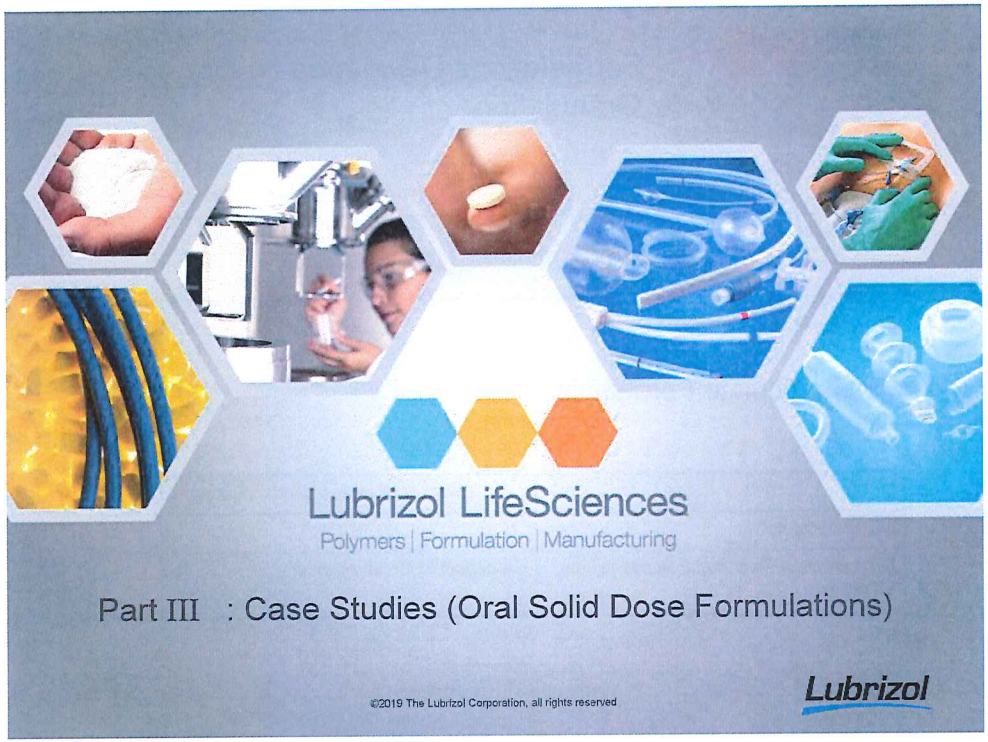
- Wang, L., Cui, F.D., hayase, T., Sunada, H. "Preparation and evaluation of solid dispersion for nitrendipine – Carbopol® and Nitrendipine-HPMCP systems using a twin screw extruder." Chem. Pharm. Bull. 53(10), 1240–1245, 2005.
- Ozawa, M., Hasegawa, K., Yonezawa, Y., Sunada, H. "Preparation of Solid Dispersion for Ethenzamide – Carbopol® and Theophylline – Carbopol® Systems Using a Twin Extruder." Chem. Pharm. Bull. 50(6), 802–807, 2002.
- Free-flowing granules containing carbomer, United States Patent 20070048364.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Potential Benefits of Carbopol® Polymers beyond Controlled Release

Lubrizol data, literature references and commercial products demonstrate benefits of Carbopol® polymers for:

- ✓ Bioadhesion
- ✓ Suspending agent (freeze drying)
- ✓ Control of microenvironmental pH
- ✓ Taste masking
- ✓ Inhibition of proteolytic enzymes
- ✓ Gastric floating systems
- ✓ Hot Melt Extrusion



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Part III : Case Studies - Oral Solid Dose Formulations

Outline

- The Biopharmaceutics Classification System
- Case studies
  - Formulations developed by aqueous granulation
  - Formulations developed by non aqueous granulation
  - Formulations developed by Hydro alcoholic granulation
  - Formulations developed by dry granulation
  - Multiparticulate formulation
- Summary
- References

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Polymers Formulation Manufacturing

APIs (as per BCS Classification) formulated as Tablets or Capsules with Carbomers or Polycarbophils

BCS Class I (HS HP) Dissolution Rate > Gastric Emptying Time • Diltiazem • Guaifenesin • Cloxacillin* • Glucosamine* • Loratadine* • Lorazepam*	**BCS Class II (LS HP)** Dissolution is rate limiting • Nifedipine* • Risperidone* • Verapamil*
BCS Class III (HS LP) Absorption is rate limiting • Metformin* • Ascorbic acid* • Pseudoephedrine*	**BCS Class IV (LS LP)** In vitro dissolution is not reliable • Ciprofloxacin • Cefixime* • Mesalamine* • Nitrofurantoin*

(*) *denotes commercial products*

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Polymers Formulation Manufacturing

Formulations Developed by Aqueous Granulation

Active - Dose	Extended Release Matrix Ingredient(s)
Aqueous Granulation	
Diclofenac Sodium - 75 mg	Carbopol® 971P NF polymer
Diclofenac Sodium - 100 mg	Carbopol® 971P NF polymer and hypromellose
Quetiapine Fumarate – 200 mg	Carbopol® 971P NF polymer
Theophylline - 200 mg	Carbopol® 974P NF polymer and hypromellose
Verapamil Hydrochloride - 240 mg	Carbopol® 971P NF polymer

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Polymers Formulation Manufacturing

Formulations Developed by Non-Aqueous or Hydro-alcoholic Granulation

Active - Dose	Extended Release Matrix Ingredient(s)
Non-aqueous Granulation	
Tramadol Hydrochloride - 100 mg	Carbopol® 971P NF and 71G NF polymers
Hydro-alcoholic Granulation	
Pentoxifylline - 400 mg	Carbopol® 971P NF and 71G NF polymers

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Formulations Developed by Dry Granulation

Active - Dose	Extended Release Matrix Ingredient(s)
Dry granulation	
Trimetazidine Dihydrochloride - 35 mg	Carbopol® 974P NF polymer

Multiparticulate Formulation

Active - Dose	Extended Release Matrix Ingredient(s)
Multiparticulate	
Domperidone Extended Release pellets 30 mg.	Carbopol® 971P NF polymer

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Polymers Formulation Manufacturing

Aqueous Granulation Formulations

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study
Diclofenac Sodium 75 mg Extended Release Tablets Using Carbopol® 971P NF Polymer

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

- To develop an extended release formulation to meet the "Drug Dissolution Test 2" requirements of the USP monograph for Diclofenac Sodium extended release tablets.

Time (hours)	Amount Dissolved
1	Not more than 28%
2	Between 20% and 40%
4	Between 35% and 60%
6	Between 50% and 80%
10	Not less than 65%

USP dissolution method: Apparatus 2, 50 rpm, 900 ml pH 7.5 phosphate buffer, wire sinkers

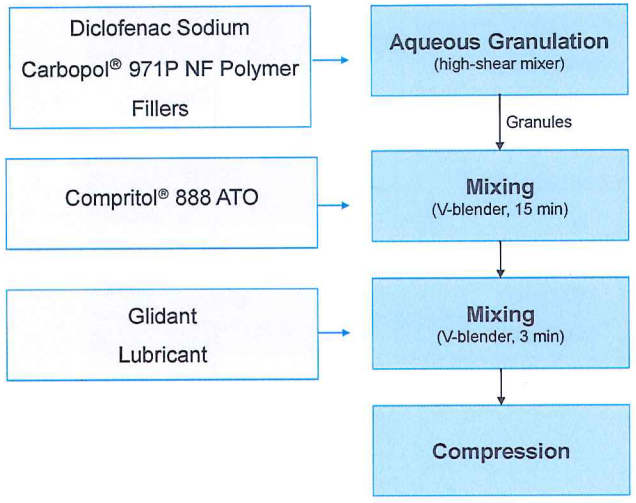
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Formulation

Ingredients	% w/w	mg/tablet
Intra-granular		
Diclofenac Sodium, USP	37.50	75.0
Carbopol® 971P NF polymer	8.00	16.0
Lactose (200 mesh)	15.00	30.0
Dibasic calcium phosphate dihydrate	30.00	60.0
Water	q.s.	
Extra-granular		
Compritol® 888 ATO	8.00	16.0
Colloidal silicon dioxide	0.50	1.0
Talc	0.50	1.0
Magnesium stearate	0.50	1.0
Total	100 %	200.0 mg

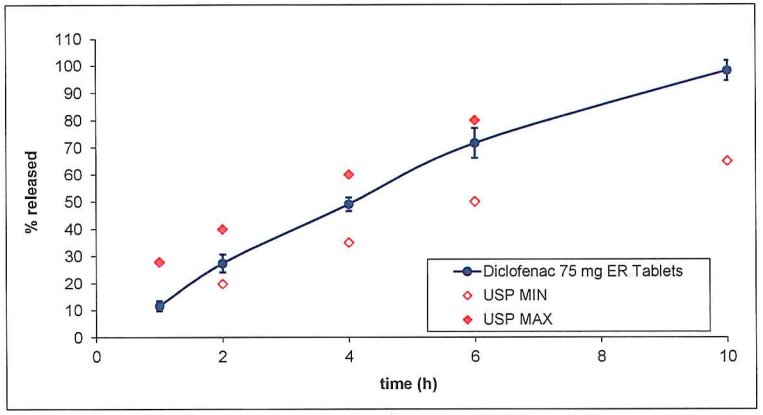
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Diclofenac Sodium Release



Diclofenac Sodium 75 mg extended release tablets were successfully formulated using Carbopol® 971P NF polymer to meet the USP requirements.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study

Diclofenac Sodium 100 mg Extended Release Tablets Using Carbopol® 971P NF Polymer and Hypromellose

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

To develop Diclofenac Sodium extended release tablets by combining Carbopol® 971P NF polymer and hypromellose.

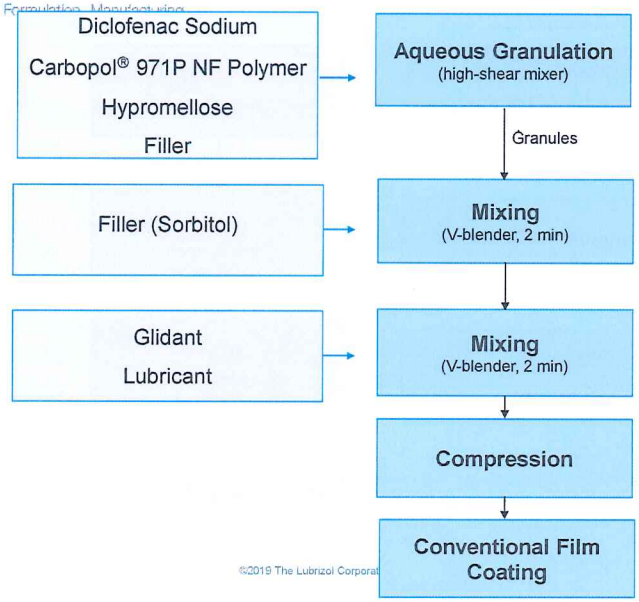
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Formulation

Ingredients	% w/w	mg/tablet
Intra-granular		
Diclofenac Sodium	34.00	100.0
Carbopol® 971P NF polymer	6.80	20.0
Hypromellose substitution type 2208 (Metolose® 90 SH-4000 SR)	5.10	15.0
Dibasic calcium phosphate dihydrate	22.10	65.0
Water	q.s.	
Extra-granular		
Sorbitol	26.19	77.0
Anhydrous silica	1.02	3.0
Magnesium stearate	1.36	4.0
Talc	1.36	4.0
Total for Core tablet		288.0
Conventional film coat	2.04	6.0
Total for Coated tablet	100.0	294.0 mg

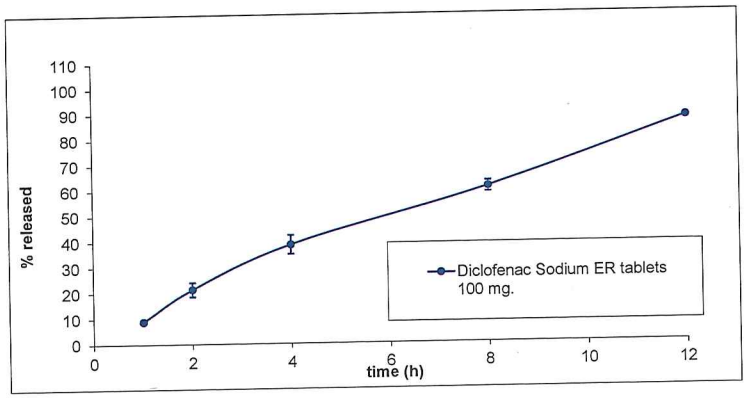
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



Lubrizol LifeSciences
Polymers Formulation Manufacturing

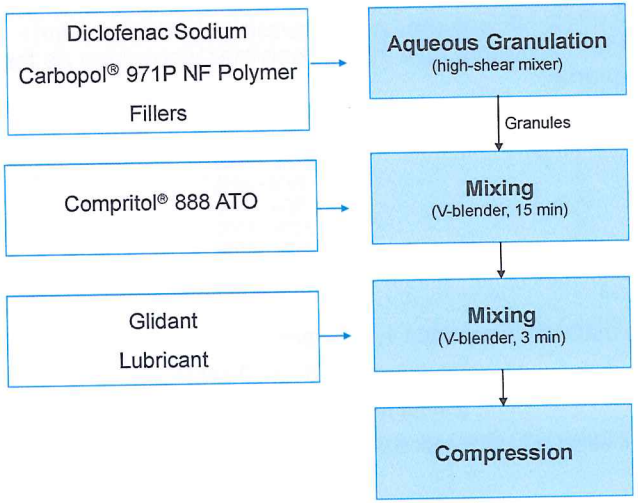
Diclofenac Sodium Release



The formulation with 6.8% w/w Carbopol® 971P NF polymer and 5.1% w/w hypromellose imparted extended release properties for up to 12 hours.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



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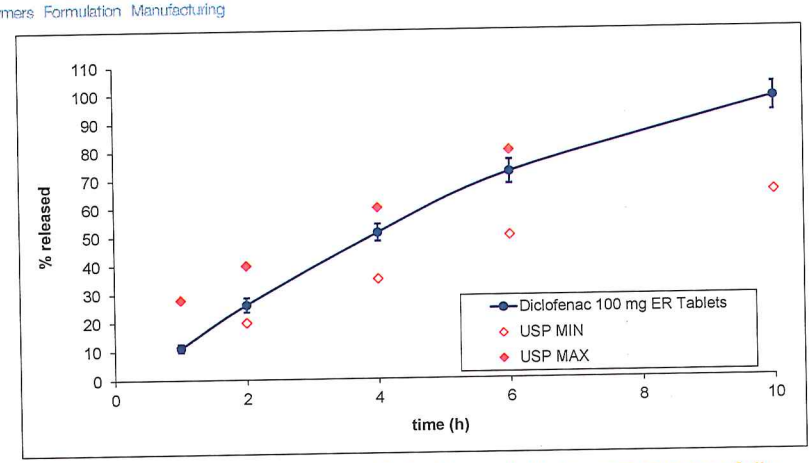
Polymers Formulation Manufacturing

Diclofenac Sodium Release



Diclofenac Sodium 100 mg extended release tablets were successfully formulated using Carbopol® 971P NF polymer to meet the USP requirements.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study

Quetiapine Fumarate 200 mg Extended Release Tablets Using Carbopol® 971P NF Polymer Coated with a Methacrylic Acid Copolymer

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

- To develop Quetiapine Fumarate extended release tablets with Carbopol® 971P NF polymer as the extended release matrix ingredient and a methacrylic acid copolymer dispersion as the film coating material.

Time (hours)	Amount Dissolved
1	10% – 30%
2	25% - 50%
4	35% - 60%
8	40% - 65%
16	60% - 90%
24	NLT 85 %

Dissolution method*: Apparatus 1, 100 rpm

0 – 2 hours: 750 ml 0.1N HCl

2 – 24 hours: 1000 ml pH 6.2 phosphate buffer

*dissolution method per US Patent 5,948,437

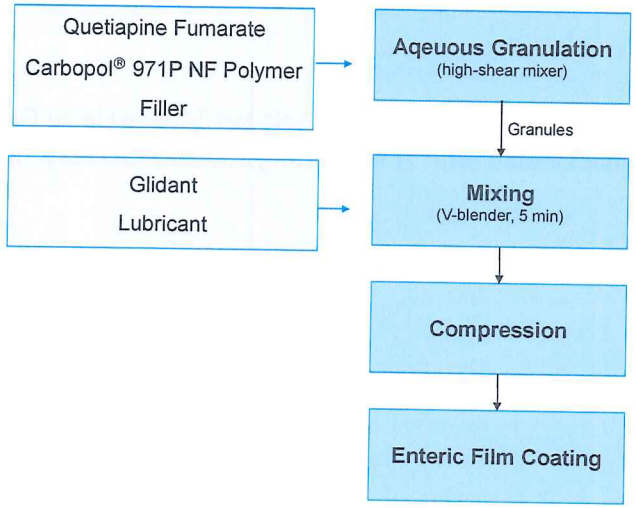
Lubrizol LifeSciences
Polymers

Experimental Formulation

Ingredients	% w/w	mg/tablet
Tablet Cores		
Quetiapine Fumarate	40.64	230.0
Carbopol® 971P NF polymer	4.42	25.0
Lactose (200 mesh)	53.00	300.0
Talc	0.97	5.50
Magnesium stearate	0.97	5.50
Water	q.s.	q.s
Total Core Tablets	*100*	*566.0*
Coating Dispersion		
Methacrylic acid copolymer dispersion (Eudragit® L 30 D-55)	22.93	9.0
Lactose (200 mesh)	11.46	15.0
Talc	1.71	2.24
Triethyl citrate	0.69	0.90
FD&C yellow #6	0.46	0.60
Titanium dioxide	0.28	0.37
Water	q.s.	q.s.
Total Coating	*100.0*	*28.11*
Total Coated Tablets		594.11

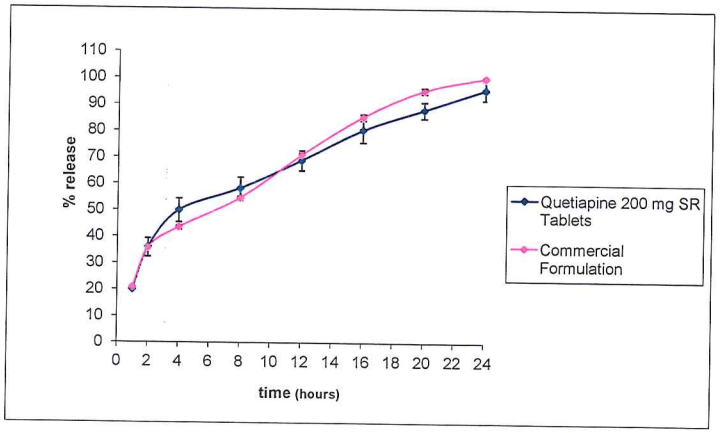
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Quetiapine Fumarate Release



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Conclusions

- Quetiapine Fumarate extended release tablets were developed with Carbopol® 971P NF polymer as the extended release matrix ingredient and a methacrylic acid copolymer dispersion as the film coating material.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study

Theophylline 200 mg Extended Release Tablets Using Carbopol® 974P NF Polymer and Hypromellose

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

- To develop an extended release formulation to meet the "Drug Dissolution Test 2" requirements of the USP monograph for Theophylline extended release capsules.

Time (hours)	Amount Dissolved
1	Between 10% - 30%
2	Between 30% - 55%
4	Between 55% - 80%
8	Not less than 80%

USP dissolution method: Apparatus 2, 75 rpm, 900 ml pH 4.5 phosphate buffer.

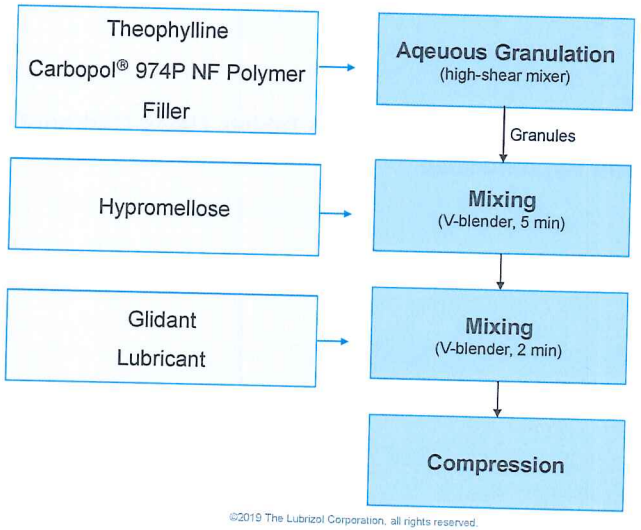
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Formulations

Ingredients	% w/w	mg/tablet
Intra-granular		
Theophylline anhydrous, USP	66.67	200.0
Carbopol® 974P NF polymer	5.00	15.0
Microcrystalline cellulose (Avicel® PH 102)	20.34	61.0
Purified water	q.s.	q.s.
Extra-granular		
Hypromellose substitution type 2208 (Metolose® 90 SH–4000 SR)	4.00	12.0
Colloidal silicon dioxide	1.33	4.0
Magnesium stearate	1.33	4.0
Talc	1.33	4.0
Total	*100*	
Tablet weight (mg)		300.0

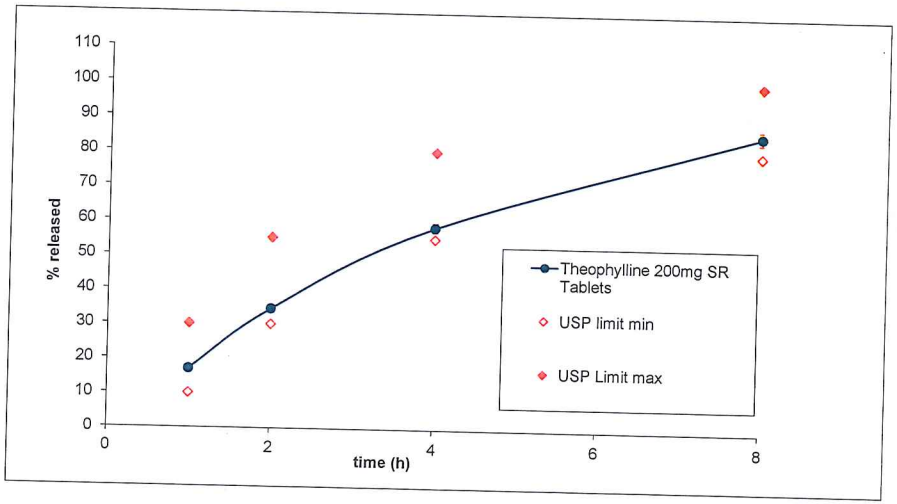
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Theophylline Release from Formulation



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Conclusions

- Theophylline extended release tablets were developed by combining Carbopol® 974P NF polymer and Metolose® 90 SH-4000 SR.
- Processing by aqueous granulation was easy due to relatively low level of hydrophilic polymers (less than 10%).

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study

Verapamil Hydrochloride 240 mg Extended Release Tablets Using Carbopol® 971P NF Polymer

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

- To develop an extended release formulation to meet the "Drug Dissolution Test 3" requirements of the USP monograph for Verapamil Hydrochloride extended release tablets.

Time (hours)	Amount Dissolved
1	Between 8% and 20%
2	Between 15% and 35%
3.5	Between 27% and 57%
5	Between 45% and 75%
8	Not less than 80%

USP dissolution method: Apparatus 2, 50 rpm, 1 hour in 900 ml 0.1N HCl followed by 7 hours in 900 ml pH 6.8 buffer with sinkers

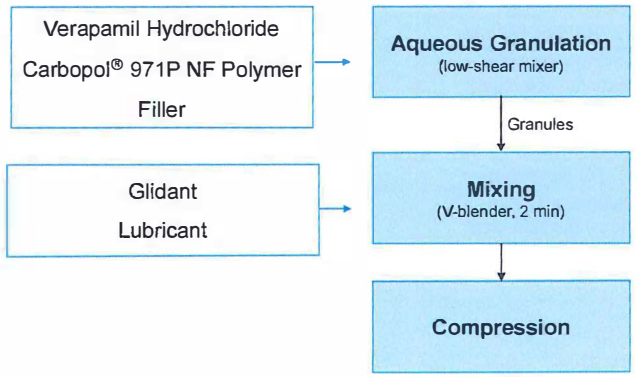
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Formulation

Ingredients	% w/w	Mg/tablet
Intra-granular		
Verapamil Hydrochloride, USP	39.22	240.0
Carbopol® 971P NF polymer	4.90	30.0
Microcrystalline cellulose (Avicel® PH-101)	53.92	330.0
Purified water	q.s.	q.s.
Extra-granular		
Magnesium stearate	0.82	5.0
Talc	0.57	3.5
Colloidal silicon dioxide	0.57	3.5
Total	*100*	
Tablet weight (mg)		612.0

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



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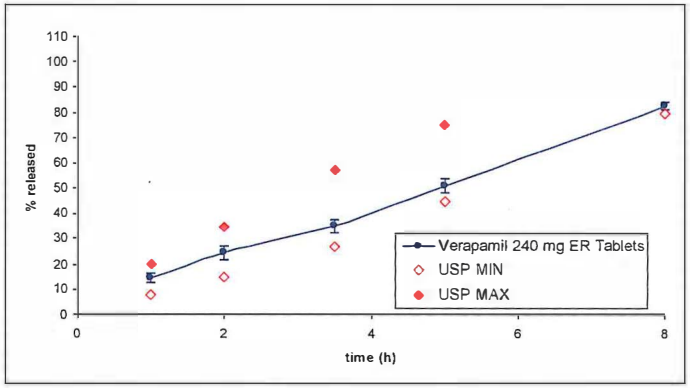
Polymers Formulation Manufacturing

Verapamil Hydrochloride Release



Verapamil Hydrochloride 240 mg extended release tablets were successfully formulated using Carbopol® 971P NF polymer to meet the USP requirements.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Non-Aqueous Granulation Formulations

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study

Tramadol Hydrochloride 100 mg Extended Release Tablets Using Carbopol® 971P NF and 71G NF Polymers

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

- To develop Tramadol Hydrochloride extended release tablets by using Carbopol® 971P NF and 71G NF polymers.

  Dissolution: USP Apparatus 1, 100 rpm, 900 ml pH 6.8 phosphate buffer

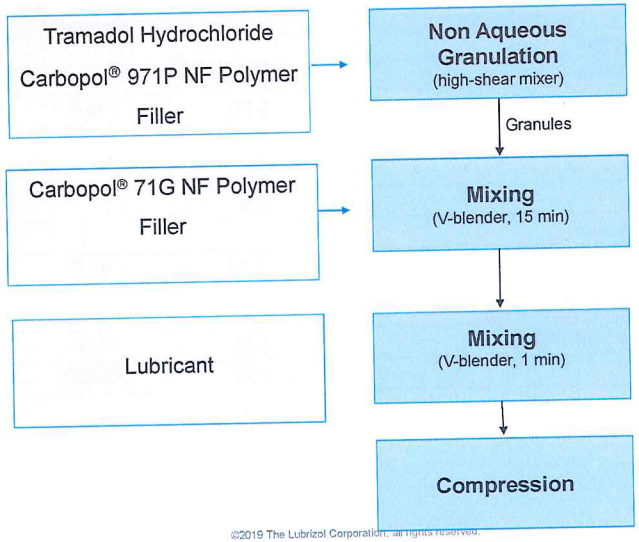
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Formulation

Ingredients	% w/w	mg/tablet
Intra-granular		
Tramadol Hydrochloride, USP	33.33	100
Carbopol® 971P NF polymer	13.00	39.0
Microcrystalline cellulose (50 µm mean particle size)	22.17	66.50
Ethyl alcohol, USP	q.s.	
Extra-granular		
Carbopol® 71G NF polymer	16.00	48.0
Microcrystalline cellulose (100 µm mean particle size)	15.00	45.0
Magnesium stearate	0.50	1.50
Total	*100*	*300.0*

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



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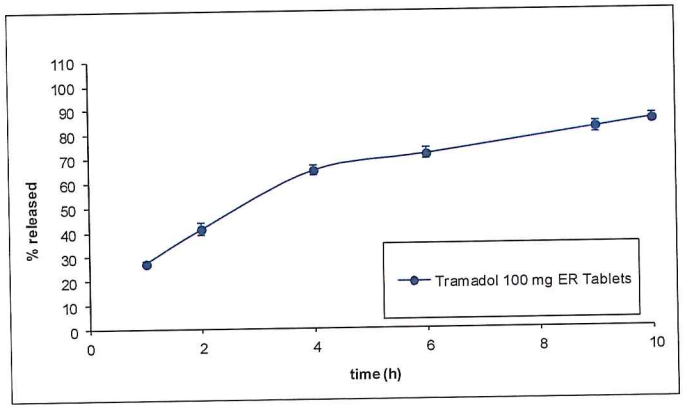
Polymers Formulation Manufacturing

Tramadol Hydrochloride Release



Tramadol Hydrochloride 100 mg extended release tablets were successfully formulated using Carbopol® 971P NF and 71G NF polymers.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Hydro-alcoholic Granulation Formulation

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study
Pentoxifylline 400 mg Extended Release Tablets Using Carbopol® 971P NF and Carbopol® 71G NF Polymers

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

- To develop an extended release formulation to meet the "Drug Release Test 1" requirements of the USP monograph for Pentoxifylline extended release tablets.

Time (h)	Amount Dissolved
1	Not more than 30%
4	Between 30% and 55%
8	Not less than 60%
12	Not less than 80%

USP dissolution method: Apparatus 2, 100 rpm, 900 ml water

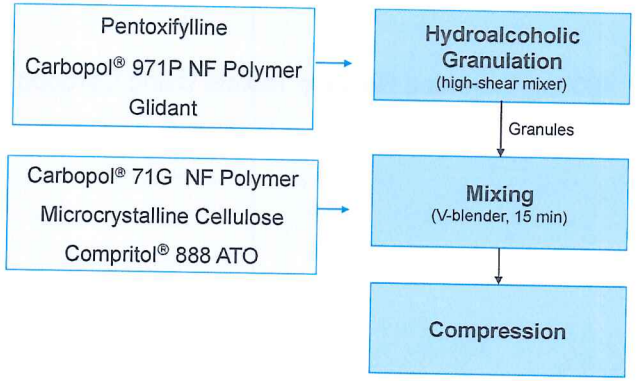
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Formulation

Ingredients	% w/w	mg/tablet
Intra-granular		
Pentoxifylline	66.67	400.0
Carbopol® 971P NF polymer	5.00	30.0
Silicon dioxide	0.50	3.0
Ethanol	q.s.	
Water	q.s.	
Extra-granular		
Carbopol® 71G NF polymer	15.00	90.0
Microcrystalline cellulose (100 µm mean particle size)	11.83	71.0
Compritol® 888 ATO	1.00	6.0
Total	*100*	*600.0*

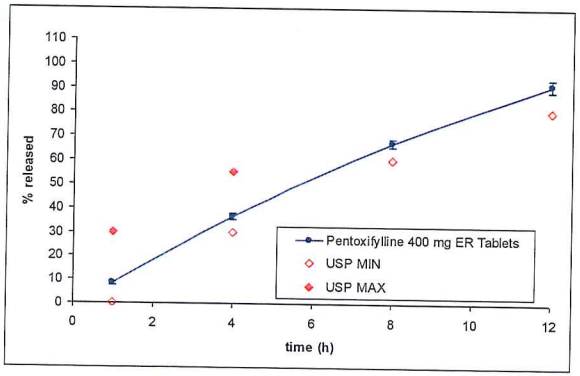
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Pentoxifylline Release



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Conclusions

- Pentoxifylline extended release tablets were developed using Carbopol® 71G NF and Carbopol® 971P NF polymers.
- Pentoxifylline release was within the USP requirements.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Dry Granulation Formulations

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study
Trimetazidine Dihydrochloride 35 mg Extended Release Tablets Using Carbopol® 974P NF Polymer

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

- To develop Trimetazidine Dihydrochloride extended release tablets with Carbopol® 974P NF polymer as the extended release matrix ingredient.

Time (h)	Amount Dissolved
1	Between 30 % to 65 %
4	Between 70 % to 90 %
10	Not less than 85 %

Dissolution method: USP apparatus 2, 50 RPM
0 - 1 hour: 750 ml 0.1 N HCl,
1 – 10 hours: 1000 ml pH 6.8 phosphate buffer

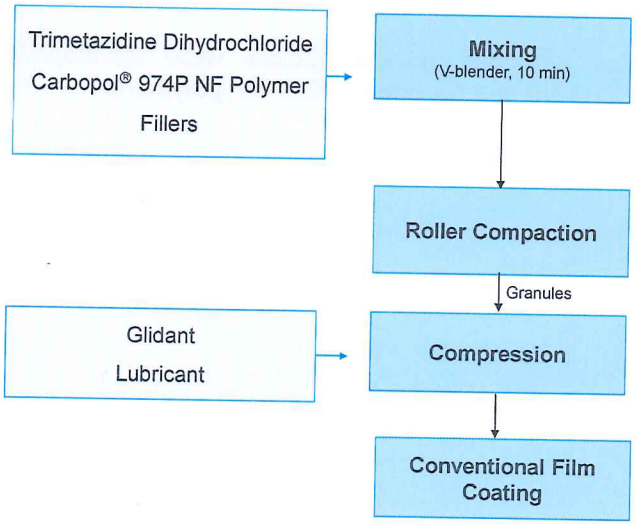
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Formulation

Ingredients	% w/w	mg/tablet
Intra-granular		
Trimetazidine Dihydrochloride	14.90	35.0
Carbopol® 974P NF polymer	21.28	50.0
Dibasic calcium phosphate, anhydrous granular	38.30	90.0
Lactose, anhydrous, granular	22.97	54.0
Colloidal silicon dioxide	0.425	1.0
Magnesium stearate	0.425	1.0
Extra-granular		
Colloidal silicon dioxide	0.425	1.0
Magnesium stearate	0.425	1.0
Talc	0.850	2.0
Total Core tablet weight	100	235.0
Conventional film coat	4.08	10.0
Total Coated tablet weight		245 mg

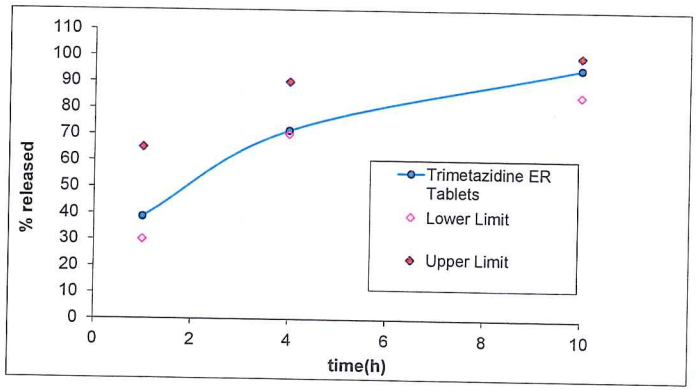
Lubrizol LifeSciences
Polymers Formulation Manufacturing

Experimental Procedure



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Trimetazidine Dihydrochloride Release



Lubrizol LifeSciences
Polymers Formulation Manufacturing

Conclusions

- Trimetazidine dihydrochloride extended release tablets were developed using Carbopol® 974P NF polymer.

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Case Study
Domperidone Extended Release pellets using Carbopol® 971P NF polymer

Lubrizol LifeSciences
Polymers Formulation Manufacturing

Objective

- To develop Domperidone extended release pellets with Carbopol® 971P NF polymer as the extended release matrix ingredient and using the innovative "powder layering" technique

Time (h)	Amount Dissolved
1	Between 15 % to 40 %
4	Between 30 % to 60 %
8	Between 55 % and 85 %
12	Not Less Than 70 %

Dissolution method: USP apparatus 2, 100 RPM in 0.1 N HCl

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Experimental Formulation

Ingredients	% w/w	mg/Dose
Stage 1: Domperidone 50 % w/w IR pellets		
Sugar Spheres	41.0	41.0
Domperidone IP	51.0	51.0
Purified Talc	2.40	2.40
Polyvinyl Pyrrolidone K 30	4.90	4.90
Sunset Yellow Supra colour	0.70	0.70
Isopropyl Alcohol (Removed during process)	q.s.	----
Stage 2: Domperidone ER pellets		
Domperidone 50 % IR Pellets from stage 1 Equivalent to Domperidone 28 % w/w	50.50	50.50
Anhydrous Dicalcium Phosphate	28.0	28.0
Carbopol® 971P NF (Carbomer Homopolymer Type A USP NF)	1.50	1.50
Talc	15.20	15.20
Polyvinylpyrrolidone K 30	4.10	4.10
Sunset Yellow Supra colour	0.70	0.70
Isopropyl Alcohol (Removed during process)	q.s	--------

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Experimental Procedure

Sugar Spheres + Blend of Domperidone and Talc → Spray of PVP K 30 in IPA and colour → 50 % W/W Domperidone IR pellets

50 % w/w IR Pellets + Blend of Carbopol® 971P NF, Talc and anhydrous DCP → Spray of PVP K 30 in IPA and colour → 30 % W/W Domperidone ER pellets

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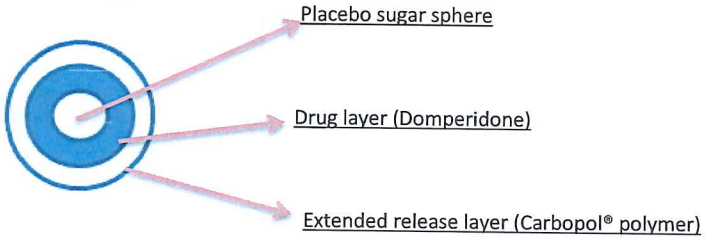
Schematic representation of pellets

Schematic representation of the pellets:



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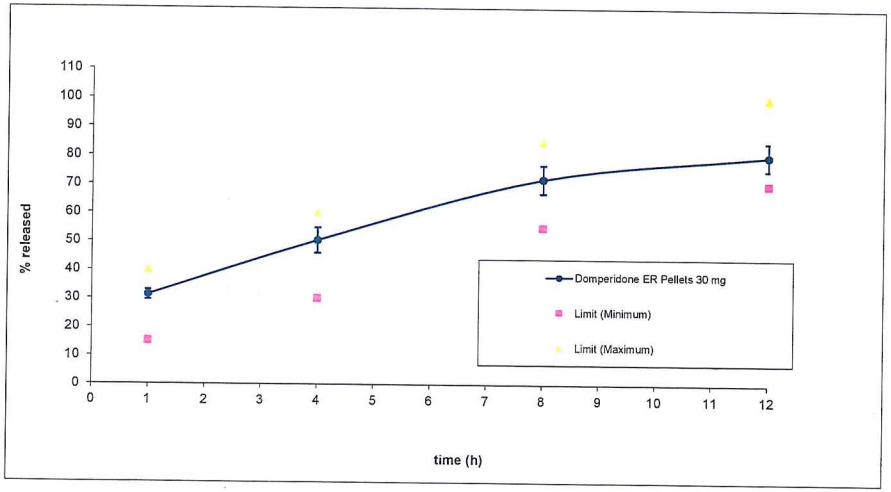
Domperidone Release profile



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Conclusion

- Domperidone extended release pellets were developed using Carbopol® 971P NF polymer and the powder layering process.
- Carbopol® polymers' very fine particle size and spherical shape ensure good uniformity of distribution even at a low inclusion level of 1.5 % and give round, smooth and hard pellets.
- Usually ethyl cellulose and HPMC are used for controlling drug release. This new technique offers superior alternative as results are consistent and process requires less time.

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Summary

- Carbopol polymers are in use for of all four BCS class APIs.
- Carbopol polymers are compatible with all the commonly used excipients
- Carbopol polymers can be processed by various manufacturing processes commonly used in oral solid dose formulations
- Carbopol polymers can be combined with other extended release, hydrophobic or enteric polymers
- The examples shown used Carbopol polymer inclusion levels from as low as 4.5 to 5.0 % in case of Quetiapine Fumarate and Verapamil HCl ER tablets to as high as 29.0 % to 30.0 % in case of Metoprolol Tartarate and Tramadol HCl ER Tablets.
- Application in Domperidone pellets exhibits the versatility of Carbopol® polymers.

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